Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Future Cardiovascular Disease Risk for Women With Gestational Hypertension: A Systematic Review and Meta-Analysis

Charmaine Chu Wen Lo, MMed (ClinEpi)*; Andre C. Q. Lo *; Shu Hui Leow; Grace Fisher; Beth Corker, BSc; Olivia Batho; Bethan Morris; Monika Chowaniec; Catherine J. Vladutiu, PhD; Abigail Fraser, PhD; Clare Oliver-Williams, PhD

BACKGROUND: Inconsistent findings have been found among studies evaluating the risk of cardiovascular disease for women who have had pregnancies complicated by gestational hypertension (the new onset of high blood pressure without proteinuria during pregnancy). We provide a comprehensive review of studies to quantify the association between gestational hypertension and cardiovascular events in women.

METHODS AND RESULTS: We conducted a systematic search of PubMed, Embase, and Web of Science in March 2019 for studies examining the association between gestational hypertension and any cardiovascular event. Two reviewers independently assessed the abstracts and full-text articles. Study characteristics and the relative risk (RR) of cardiovascular events associated with gestational hypertension were extracted from the eligible studies. Where appropriate, the estimates were pooled with inverse variance weighted random-effects meta-analysis. A total of 21 studies involving 3 60 1192 women (127 913 with gestational hypertension) were identified. Gestational hypertension in the first pregnancy was associated with a greater risk of overall cardiovascular disease (RR, 1.45; 95% CI, 1.17–1.80) and coronary heart disease (RR, 1.46; 95% CI, 1.23–1.73), but not stroke (RR, 1.26; 95% CI, 0.96–1.65) or thromboembolic events (RR, 0.88; 95% CI, 0.73–1.07). Women with 1 or more pregnancies affected by gestational hypertension were at greater risk of cardiovascular disease (RR, 1.81; 95% CI, 1.42–2.31), coronary heart disease (RR, 1.83; 95% CI, 1.33–2.51), and heart failure (RR, 1.77; 95% CI, 1.47–2.13), but not stroke (RR, 1.50; 95% CI, 0.75–2.99).

CONCLUSIONS: Gestational hypertension is associated with a greater risk of overall cardiovascular disease, coronary heart disease, and heart failure. More research is needed to assess the presence of a dose–response relationship between gestational hypertension and subsequent cardiovascular disease.

REGISTRATION: URL: https://www.crd.york.ac.uk/prospero/; Unique identifier: CRD42018119031.

Key Words: cardiovascular disease ■ gestational hypertension ■ pregnancy ■ review ■ women

Gestational hypertension (GH), also known as pregnancy-induced hypertension, is defined as the onset of high blood pressure (at least 140 mm Hg systolic or 90 mm Hg diastolic) without proteinuria on 2 occasions at least 4 hours apart in an ordinarily normotensive pregnant woman after 20 weeks of gestation.[1,2] Rates of GH vary between countries, with 1% to 6% of pregnancies complicated by GH in Western countries.[3,4]

Pregnancy-induced hypertension is increasingly recognized as a risk factor for subsequent cardiovascular disease (CVD) in women.[5] In particular,

Correspondence to: Clare Oliver-Williams, PhD, Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom. E-mail: cto21@medschl.cam.ac.uk

Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013991

*Miss C.C.W. Lo and Mr A.C.Q. Lo contributed equally to this work and are cofirst authors.

For Sources of Funding and Disclosures, see page 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- In a systematic review of >3 million women, we found that gestational hypertension is associated with a greater risk of cardiovascular disease, coronary heart disease, and heart failure.
- Nonsignificant trends toward a greater risk of stroke after gestational hypertension were found.

What Are the Clinical Implications?

- Women with a pregnancy complicated by gestational hypertension are at greater risk of developing several different kinds of cardiovascular disease.
- Women who experience gestational hypertension may benefit from counseling during and/or after pregnancy about their long-term cardiovascular risk.

Nonstandard Abbreviations and Acronyms

ARI	absolute risk increases
CHD	coronary heart disease
CVD	cardiovascular disease
GH	gestational hypertension
HR	hazard ratio
ICD	*International Classification of Diseases*
IRR	incident rate ratio
MI	myocardial infarction
OR	odds ratio
RR	relative risk

pre-eclampsia, characterized by GH with proteinuria, is associated with a markedly higher CVD risk[6–8] and has been incorporated in the American Heart Association guidelines for the assessment of CVD risk in women.[9] It is unclear if GH and pre-eclampsia are manifestations of different severities of the same pathophysiological mechanism or represent separate pathologies.[10] Therefore, the raised CVD risk in women with a history of pre-eclampsia may not be representative of the risk associated with GH.

Studies that have assessed the CVD risk associated with GH have found mixed results. Results have ranged from no raised risk[11–13] to more than twice the risk of some cardiovascular events.[13–18] This lack of clarity about the long-term cardiovascular risk for women who have had GH without proteinuria is further underscored by calls for further research into this area by the UK's National Institute for Health and Care Excellence.[19] Consequently, we conducted a systematic review and meta-analysis of prospective studies to evaluate the risk of a range of cardiovascular events for women after 1 or more pregnancies complicated by GH.

METHODS

The design, implementation, analysis, and reporting for this systematic review and meta-analysis are in accordance with the Meta-Analysis of Observational Studies in Epidemiology[20] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses[21] protocols (Tables S1 and S2). An internal study protocol was developed to perform this review, which is registered on PROSPERO (https://www.crd.york.ac.uk/prospero/; review reference number CRD42018119031).[22] The authors declare that all supporting data are available within the article and its online supplementary files.

Search Strategy and Selection Criteria

We searched the databases PubMed, Embase, and Web of Science in March 2019. No restrictions were applied to the language or publication period of the articles. Both medical search headings and open-text fields were used to identify articles.

The exposure was GH and any cardiovascular outcome was of interest, including (1) overall CVD; (2) coronary heart disease (CHD); (3) any stroke, including ischemic and hemorrhagic stroke; (4) heart failure; and (5) thromboembolic events. The details of the search terms are provided in Table S3. The search in PubMed was restricted to articles relating to humans. We cross-referenced the bibliographies of any relevant journal articles and systematic reviews we identified during our search to determine if there were any additional studies not found in our original search that fit our inclusion criteria.

To be included in the review, the articles had to compare the risk of at least 1 cardiovascular outcome for women with previous GH with that of women who had 1 or more normotensive pregnancies. GH was defined as a new onset of systolic and/or diastolic hypertension after 20 weeks gestation without proteinuria. Events had to occur more than 1-year postpartum to minimize the risk of comorbidity. Articles only evaluating pre-eclampsia, or combining both pre-eclampsia and GH as an exposure, were excluded to minimize heterogeneity in the exposure. Study designs were limited to cohort studies and case-control studies. Exclusion criteria were the following: (1) studies that included animals, men, children, or nulliparous women; (2) studies that did

not have a cardiovascular outcome; (3) studies that combined women with GH and women with preeclampsia; and (4) studies that did not evaluate GH as an independent exposure.

Selection of Studies and Data Extraction

Using the software Abstrackr,[23] each abstract found with our search strategy were screened by 2 authors (C.C.W.L., A.C.Q.L., S.H.L., G.F., B.C., O.B., B.M., or M.C.). Any differences between reviewers were discussed and resolved by a third individual (C.O.-W.). For relevant abstracts, full texts were accessed to determine their eligibility for the review. Where 2 studies evaluated the same outcome in the same cohort, the study with the longer follow-up time was used. Data on the follow-up period, study design, population characteristics, sample size, exposure and outcome, methods of ascertainment for GH and cardiovascular events, and adjustment factors were abstracted and independently verified by a second author. Both minimally adjusted and fully adjusted measures of the association and 95% CIs were also extracted and verified. Any differences between reviewers were discussed and resolved by a third author.

For the fully adjusted measures of association, studies were categorized as poorly, adequately, or well adjusted. To be considered well adjusted, studies had to control for maternal age; socioeconomic factors; obstetric history, including pregnancy complications other than GH; and chronic diseases. We selected these categories as they broadly cover most potential confounders and are representative of the range of adjustments made in the studies included in the review. Adequately adjusted studies controlled for variables from 3 of these 4 categories, and poorly adjusted studies controlled for variables in 2 or fewer categories.

Two authors independently evaluated the bias within each individual study using the validated Newcastle–Ottawa Scale, a semiquantitative scale designed to evaluate the quality of nonrandomized studies.[24] It allocates a maximum of 9 stars to a study. Study quality was judged on the selection criteria of participants, comparability of groups through adjustment, and exposure or outcome assessment.

Statistical Analysis

The included studies used 2 different approaches to classify GH exposure. The first approach classified women based on the presence or absence of a diagnosis of GH in the first pregnancy. The second approach classified women as having either a history of 1 or more pregnancies affected by GH or only having normotensive pregnancies. Because of the distinction between these 2 classifications, our meta-analyses were conducted assessing risk associated with 2 exposures: (1) a diagnosis of GH in the first pregnancy and (2) a history of 1 or more pregnancies affected by GH.

For a meta-analysis to be conducted, it was necessary to identify a minimum of 3 studies evaluating the risk of a particular cardiovascular outcome (eg, stroke, CHD) associated with 1 of these exposures. If fewer than 3 studies were found for an exposure–outcome combination, then the results were included in the systematic literature review, but not in the meta-analysis.

For studies that reported separate relative risk (RR) estimates for subgroups (eg ethnic groups) or that reported CHD and overall stroke risk estimates separately for the same population, but did not report an overall CVD risk estimate, we used inverse variance weighted fixed effects meta-analysis to generate overall study-level RRs before combining these results with those from other studies.

When pooling the results from separate studies, the inverse variance weighted method was used to combine odds ratio (OR), RR, and hazard ratios (HR) to produce a pooled RR under the rare outcome assumption. Random effects analyses using the DerSimonian–Laird model were used to allow for between-study heterogeneity as there were clear differences between the identified studies, such as ethnicity. Heterogeneity was assessed using the Cochrane χ^2 statistic and the I^2 statistic. Individual RR estimates and summary estimates were displayed graphically with forest plots.

To assess the number of cases that could be avoided if effective intervention for CVD are targeted to women with GH, the absolute risk increases (ARI) for overall CVD and CHD were calculated separately for both exposures. The equation ARI=(RR−1)×(assumed control risk) was used, where RR is from the meta-analysis.

Female-specific European Heart Network statistics for 2015 were used to estimate the assumed control risk (ie, the incidence) of overall CVD and CHD because the largest number of studies came from Europe.[25] ARI were expressed as events per 1000 woman-years of follow-up. It was not possible to calculate the ARI for heart failure or thromboembolic events as we could not obtain estimates of their incidence. The ARI was not calculated for stroke because of the nonsignificant results in the main meta-analyses.

Sensitivity Analyses

A number of sensitivity analyses were conducted. The first analysis excluded studies with the largest effect estimates to assess the impact of these studies on the

magnitude of the pooled result and the observed heterogeneity. The second analysis included all studies and reran all meta-analyses with fixed effects models. This was performed because the DerSimonian–Laird method for random effects meta-analysis may have statistical limitations in the case of few studies.[26] Therefore a fixed effects meta-analysis will provide an assessment of the consistency of the results and an estimation of the relationships specifically in the overall populations studied. Several studies assessed the risk of stroke subtypes (intracerebral hemorrhage and ischemic stroke) associated with a history of GH. To assess the risk of any stroke outcome, an additional meta-analysis was conducted that combined risk estimates for overall stroke and stroke subtypes associated with a history of GH.

A total of 5 stratified analyses were conducted to evaluate (1) the effect of different levels of adjustment, (2) the potential impact of bias in individual studies, and (3) the effect of study-level characteristics on the association between GH and overall CVD. Only overall CVD was assessed as an outcome because too few studies were included in the meta-analyses of other events. Analyses were stratified by (1) level of adjustment, (2) risk of bias, (3) duration of follow-up, (4) year of publication, and (5) the population studied. In these analyses, we tested for trend across strata using random effects meta-regression.

Small study effects were evaluated through funnel plots and Egger tests for meta-analyses including 6 or more studies.[27] Upon evidence of funnel plot asymmetry and indication of significant bias from the Egger test, the trim-and-fill method was used to correct for funnel plot asymmetry.[28]

All tests were 2-tailed and P values of <0.05 were considered statistically significant. STATA software package (version 14.2; Stata Corp, College Station, TX) was used for all statistical analyses.

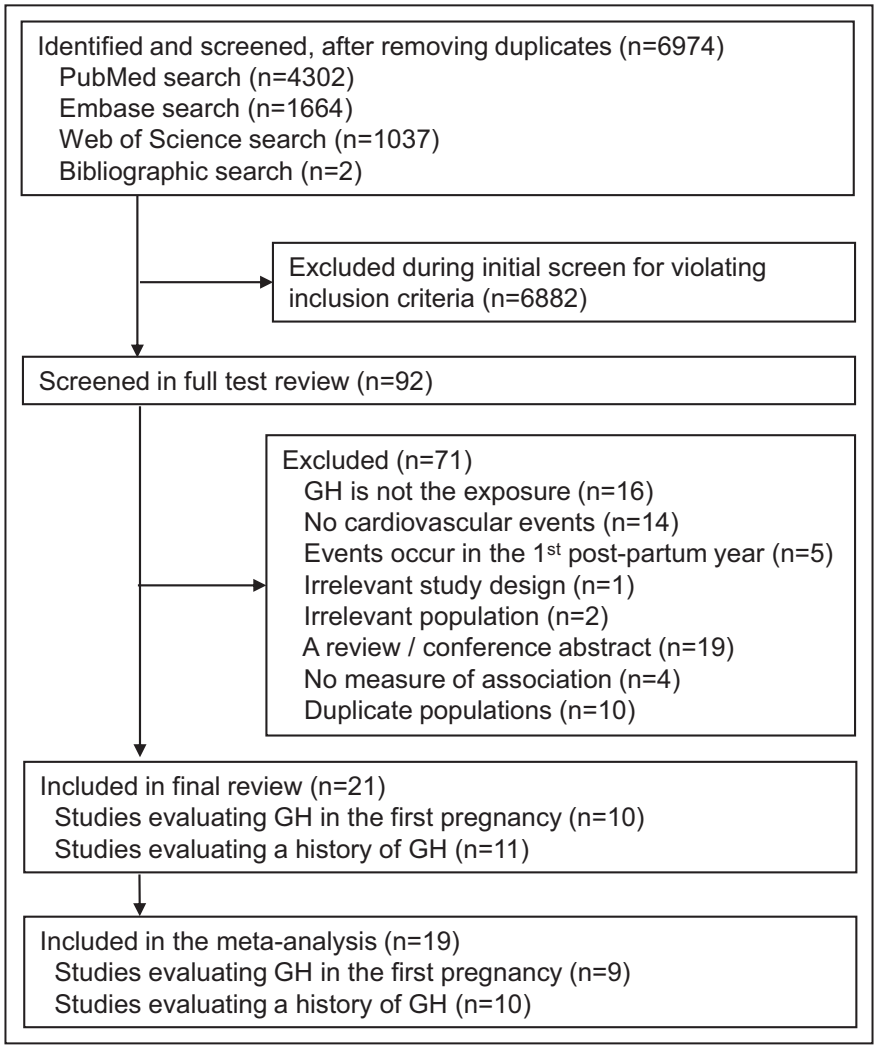


Figure 1. Identification of studies included in the review of GH and risk of cardiovascular events.
GH indicates gestational hypertension.

RESULTS

Our search strategy identified 6974 studies, of which 6882 were excluded during the initial abstract screen. The remaining 92 articles were reviewed in full, resulting in 71 being excluded and 21 included in our final review (Figure 1). The studies included 3 601 192 women, with 127 913 women with a history of 1 or more pregnancies affected by gestational hypertension from 18 cohort studies[11–13,29–39] and 3 nested case-control studies.[15,18,40] Studies were conducted in Europe (12 studies*) and North America (5 studies[15,17,31,32,36]) as well as in Taiwan (2 studies[18,41]) and Australia (1 study[13]) (Table).

All of the studies ascertained GH and cardiovascular events through medical records, registry data, or health insurance claims (Table, Table S4). The duration of follow-up varied from a median of 4.5 years[16] to a maximum of 73 years[17] (Table). Based on the Newcastle–Ottawa scale, 5 studies were judged to be at high risk of bias, and 10 studies provided risk estimates that were poorly adjusted (Tables S5 and S6).

GH in the First Pregnancy

A total of 11 studies,[11,12,14,31,33,34,36–40] including 3 209 836 women (74 066 with GH), examined the risk of cardiovascular events in women whose first pregnancy was affected by GH. The risk of the following events was assessed: overall CVD, CHD, heart failure, any stroke, myocardial infarction (MI), thromboembolic events, angina, other circulatory disease, and a combined outcome of acute MI and acute cerebral stroke (Figure 2, Tables S7 and S8). Of the 9 included cohorts, GH affected 1.0% to 27.1% of first pregnancies. Meta-analyses included 2 818 819 women (66 130 with GH) for overall CVD, 1 793 887 women (35 876 with GH) for CHD, 1 402 870 women (27 940 with GH) for stroke, and 1 402 870 women (27 940 with GH) for thromboembolic events.

Meta-analyses of adjusted estimates found a significantly greater risk of overall CVD (7 studies[11,12,14,31,34,36,37]; RR, 1.45; 95% CI, 1.17–1.80) and CHD (4 studies[11,34,37,39]; RR, 1.46; 95% CI, 1.23–1.72), but not overall stroke (3 studies[11,34,37]; RR, 1.26; 95% CI, 0.96–1.64) or thromboembolic events (3 studies[11,34,40]; RR, 0.88; 95% CI, 0.73–1.07) (Figure 3). There was evidence of significant between-study heterogeneity for overall CVD (I^2=92%, P<0.001), CHD (74%, P=0.009), and overall stroke (82%, P=0.004), but not thromboembolic events (0%, P=0.413). Meta-analyses of the unadjusted results were consistent with these findings (Figure S1).

The ARI in overall CVD and CHD associated with GH in the first pregnancy, based on the European population, were 8.6 and 4.2 events per 1000 woman-years, respectively.

Five findings from 3 studies were not included in the meta-analyses (Table S8). These studies evaluated heart failure, a composite outcome of MI and acute cerebral stroke, angina, MI, and other circulatory disease. Greater risks of heart failure and combined acute MI and acute cerebral stroke were noted, which both attenuated after adjustment (adjusted HR, 1.37; 95% CI, 0.98–1.93; and adjusted HR, 1.8; 95% CI, 0.8–4.1), respectively.[34,38] One study found no increased risk of MI (adjusted OR, 0.73; 95% CI, 0.32–1.63) or angina (adjusted OR, 1.02; 95% CI, 0.58–1.81), but noted a greater risk of other circulatory disease, defined as circulatory diseases that did not include hypertension, CHD, or cerebrovascular disease (adjusted incident rate ratio [IRR], 1.51; 95% CI, 1.06–2.14).[40]

History of GH

A total of 11 studies from 10 populations† assessed the risk of a cardiovascular outcome associated with a history of 1 or more pregnancies affected by GH. They included 2 291 304 women (73 994 with GH). The studies evaluated overall CVD, CHD, heart failure, overall stroke, intracerebral hemorrhage, ischemic stroke, MI, and thromboembolic events (Figure 1, Tables S7 and S8). Of the included studies, 9 were cohort studies in which the prevalence of women with a history of GH ranged from 1.1% to 19.0%. Meta-analyses included 861 087 women (50 356 with GH) for overall CVD, 471 454 women (35 272 with GH) for CHD, 1 126 452 women (16 800 with GH) for heart failure, and 463 911 women (34 281 with GH) for stroke.

In meta-analyses of adjusted risk estimates, a history of GH was associated with a greater risk of overall CVD (8 studies[13,15–18,29,32]; RR, 1.81; 95% CI, 1.42–2.32), CHD (4 studies[13,17,29,35]; RR, 1.83; 95% CI, 1.33–2.51) and heart failure (3 studies[13,17,29]; RR, 1.77; 95% CI, 1.47–2.13), but not overall stroke (3 studies[29,30,35]; RR, 1.50; 95% CI, 0.75–2.99) (Figure 4). There was evidence of high heterogeneity in all analyses: overall CVD (84%, P<0.001), CHD (88%, P<0.001), heart failure (63%, P=0.065), and overall stroke (70%, P=0.035). A greater CVD risk was also observed in the meta-analysis of unadjusted findings (Figure S2).

The ARI in overall CVD and CHD associated with a history of GH, based on the European population, were 15.6 and 7.6 events per 1000 woman-years, respectively.

Findings from 7 studies were not included in the meta-analysis (Table S8). These studies evaluated the risk of MI, intracerebral hemorrhage, ischemic stroke, cardiomyopathy, and thromboembolic events.

*References 11, 12, 14, 16, 29, 30, 33–35, 37–39.

†References 12, 13, 15–17, 29, 30, 32, 35, 41.

Table. Characteristics of Studies Included in the Review

First Author, y	Details of Cohort	Study Design	No. of Women	No. of Women With GH	GH Definition	Method of GH Ascertainment	Duration of Follow-Up,y	Age at Enrollment, y	Outcome(s)	Method of Outcome Ascertainment
Andolf et al 2017[29]	Swedish National Register Study 1973–2009	Cohort study	283 990	4762	*ICD* codes: *ICD-8*	Medical records	Mean: 35	Mean: 26.19	Heart failure*	Medical records
Behrens et al 2016[30]	Danish medical registries, 1978–2012	Cohort study	834 919	11 047	*ICD* codes: *ICD-8, ICD-10*	Medical records	Mean: 17.9	Median: 25–29	Cardiomyopathy	Medical records
Bhattacharya et al 2012[11]	Aberdeen Maternity and Neonatal Databank and NHS medical records, 1950–2008	Cohort study	32 828	8891	Diastolic pressure >90 mmHg on two occasions at least four hours apart or one reading of >110 mmHg	Medical records	Max: 58	Mean: 24.27	CVD, CHD, stroke, pulmonary embolism	Medical records
Cain et al 2016[31]	Florida maternal and infant databases, 1998–2009	Cohort study	302 686	17 150†	*ICD* codes *ICD-9-CM*	Medical records	Median: 4.9	Mean: 25.1	CVD	Medical records
Cirillo et al 2015[32]	US Child Health and Development Studies, 1959–2011	Cohort study	10 721	1662	≥1 blood pressure reading of >140/90 mm Hg after 20 wk gestation	Medical records	Range: 44–52	Median: 26	Fatal CVD	Death certificates
Grandi et al 2017†[14]	UK Clinical Database, 1990–2013	Cohort study	146 000	Not given	Read codes	Medical records	Median: 4.7	Mean: 29.24	CVD	Medical records
Kestenbaum et al 2003[15]	Washington State Birth Events Record Database & Comprehensive Hospital Abstract Reporting System database, 1987–2001	Nested Case Control	103 589	10 687	*ICD* codes: *ICD-9-CM*	Birth certificate data	Mean 7.8	Mean: 26.23	CVD, thromboembolic events	Medical records
Lin et al 2016[41]	Taiwan National Health Insurance Database, 2000–2013	Cohort study	36 950	7390	*ICD* codes: ***ICD-9-CM***	Health insurance claims data	Max: 13	Mean: 31.06	Intracerebral hemorrhage	Health insurance claims data
Luoto et al 2008[12]	Women giving birth in Helsinki hospitals, 1954–2005	Cohort study	4000	98	Coding not specified	Medical records	Mean: 44	Not given	Fatal CVD	Medical records

(*Continued*)

Table. Continued

First Author, y	Details of Cohort	Study Design	No. of Women	No. of Women With GH	GH Definition	Method of GH Ascertainment	Duration of Follow-Up,y	Age at Enrollment, y	Outcome(s)	Method of Outcome Ascertainment
Lykke et al 2009[34]	Danish medical registries, 1978–2007	Cohort study	782 287	7449	*ICD* codes: *ICD-8, ICD-10*	Medical records	Mean: 14.6	Mean: 26.8	CHD, heart failure, thromboembolic event, stroke	Medical records
Lykke et al 2010[33]	Danish medical registries, 1978–2007	Cohort study	782 287	7449	*ICD* codes: *ICD-8, ICD-10*	Medical records	Median: 14.8	Mean: 26.8	Fatal CVD	Medical records
Männistö et al 2013[35]	Northern Finland Birth Cohort, 1966–2000	Cohort study	7543	991	SBP ≥145 mm Hg and/or DBP ≥95 mm Hg	Assessed during pregnancy as part of study	Mean: 39.4	Mean: 26.76	CHD, MI, heart failure, stroke	Medical records
Ray et al 2005[36]	Ontario Health Insurance Plan, 1990–2004	Cohort study	963 263	20 942	*ICD* codes: *ICD9*	Healthcare administrative databases	Median 8.7	Mean: 28	CVD	Hospital database
Riise et al 2018[37]	Norweigian registries, 1980–2009	Cohort study	587 755	11 600	SBP ≥140 mm Hg, DBP ≥90 mm Hg, or >15 mm Hg BP increase measured <20 wk gestation	Medical records	Median: 14.3	Mean: 26.3	CVD, CHD, stroke	Medical records
Riise et al 2019[38]	Norweigian registries, 1980–2009	Cohort study	20 075	364	SBP ≥140 mm Hg, DBP ≥90 mm Hg, or >15 mm Hg BP increase measured <20 wk gestation	Medical Records	Median: 11.4	Mean: 26.0	Composite: acute myocardial infarction or acute cerebral stroke	Medical records
Schmiegelow et al 2014[16]	Danish registries, 2004–2009	Cohort study	273 101	2903	*ICD* codes: *ICD-8, ICD-10*	Medical records	Median: 4.5	Median: 30.4	MI, ischemic stroke, CVD	Medical records
Theilen et al 2016[17]	Utah Population Database, 1939–2012	Cohort study	152 034	28 894	Coding not specified	Birth certificates	Max: 73	Mean: 26.0	CHD, stroke	Medical records
Tooher et al 2017[13]	Royal Prince Alfred Women and Babies hospital, Australia, 1980–2009 onward	Cohort study	27 887	625	*ICD* codes: *ICD-9-AM*	Medical records	Median: 20‡	Mean: 27	CVD, CHD, stroke	Registry, discharge
Wikstrom et al 2005[39]	Swedish Medical Birth Register, 1987–2001	Cohort study	391 017	7936	*ICD* codes: *ICD-8*	Medical records	Max: 15	Range: 15–64	CHD	Registry (cause of death, hospital discharge)

(*Continued*)

Table. Continued

First Author, y	Details of Cohort	Study Design	No. of Women	No. of Women With GH	GH Definition	Method of GH Ascertainment	Duration of Follow-Up,y	Age at Enrollment, y	Outcome(s)	Method of Outcome Ascertainment
Wilson et al 2003[40]	Aberdeen Maternity and Neonatal Databank, 1951–1999	Nested case control	2394	1197	DBP ≥90 mm Hg twice at 4+ h apart or 1 reading of ≥110 mm Hg	Medical records	Max: 48	Mean: 24.2	Angina, MI, DVT, other circulatory disease (not hypertension, CHD or cerebrovascular disease)	Medical and death records
Yeh et al 2014[18]	Taiwan National Health Insurance database, 1998–2009	Nested case-control	5765	725	*ICD* codes: *ICD-9-CM*	Health insurance claims data	Median: 5.8	Mean: 29.8	CVD	Medical records

CHD indicates coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DVT, deep vein thrombosis; GH, gestational hypertension; *ICD, International Classification of Diseases*; MI, myocardial infarction; NHS, National Health Service; and SBP, systolic blood pressure.
*Stroke, CHD, and CVD also reported, but not included in the meta-analysis as the same population used in Lykke et al.[34]
†Cain et al[31] and Grandi et al[14] did not indicate how many patients had GH, and the total number of women was estimated.
‡Median time from index pregnancy to onset of CVD—no follow-up duration given for full cohort.

Figure 2. Association between gestational hypertension and cardiovascular events, showing summary RRs for the meta-analyses of each outcome.
RR indicates relative risk.

Evidence of higher risks were found for cardiomyopathy (HR, 1.83; 95% CI, 1.20–2.63), intracerebral hemorrhage (IRR, 3.62; 95% CI, 3.63–3.81) and, in 2 studies, ischemic stroke (IRR, 1.59; 95% CI, 1.24–2.04; HR, 2.78; 95% CI, 1.13–6.82).[16,30,35,41] A history of GH was also associated with MI in 1 study (IRR, 1.75; 95% CI, 1.40–2.19),[35] but not in a second study (HR, 1.41; 95% CI, 0.19–10.21).[16] No statistically strong evidence of an association between a history of GH and thromboembolic events was found (HR, 1.5; 95% CI, 0.9–2.5).[15]

Two studies assessed the dose–response relationship between number of pregnancies with GH and a cardiovascular outcome. Both identified cohorts of women with 2 pregnancies who were categorized as having (1) GH in the first pregnancy only, (2) GH in the second pregnancy only, (3) GH in both pregnancies, or (4) GH in neither pregnancy. A greater risk of overall CVD relative to normotensive women was found for women with GH in their first pregnancy (HR, 1.7; 95% CI, 1.5–2.0), their second pregnancy (HR, 2.4; 95% CI, 2.1–2.8), and in both pregnancies (HR, 1.9; 95% CI, 1.8–2.0).[37] A greater CHD risk was also noted for women with GH in either their first pregnancy (IRR, 1.9; 95% CI, 1.5–2.4) or second pregnancy (IRR, 2.4; 95% CI, 1.8–3.2) and for those with 2 or more affected pregnancies (IRR, 2.8; 95% CI, 2.0–3.9).[39]

Sensitivity Analyses

Risk estimates were consistent after excluding studies with the largest effect and after conducting a fixed effects meta-analysis, with I^2 results staying relatively constant (Table S9). When all stroke events, including overall stroke and stroke subtypes (intracerebral hemorrhage and ischemic stroke), were included in the history of GH

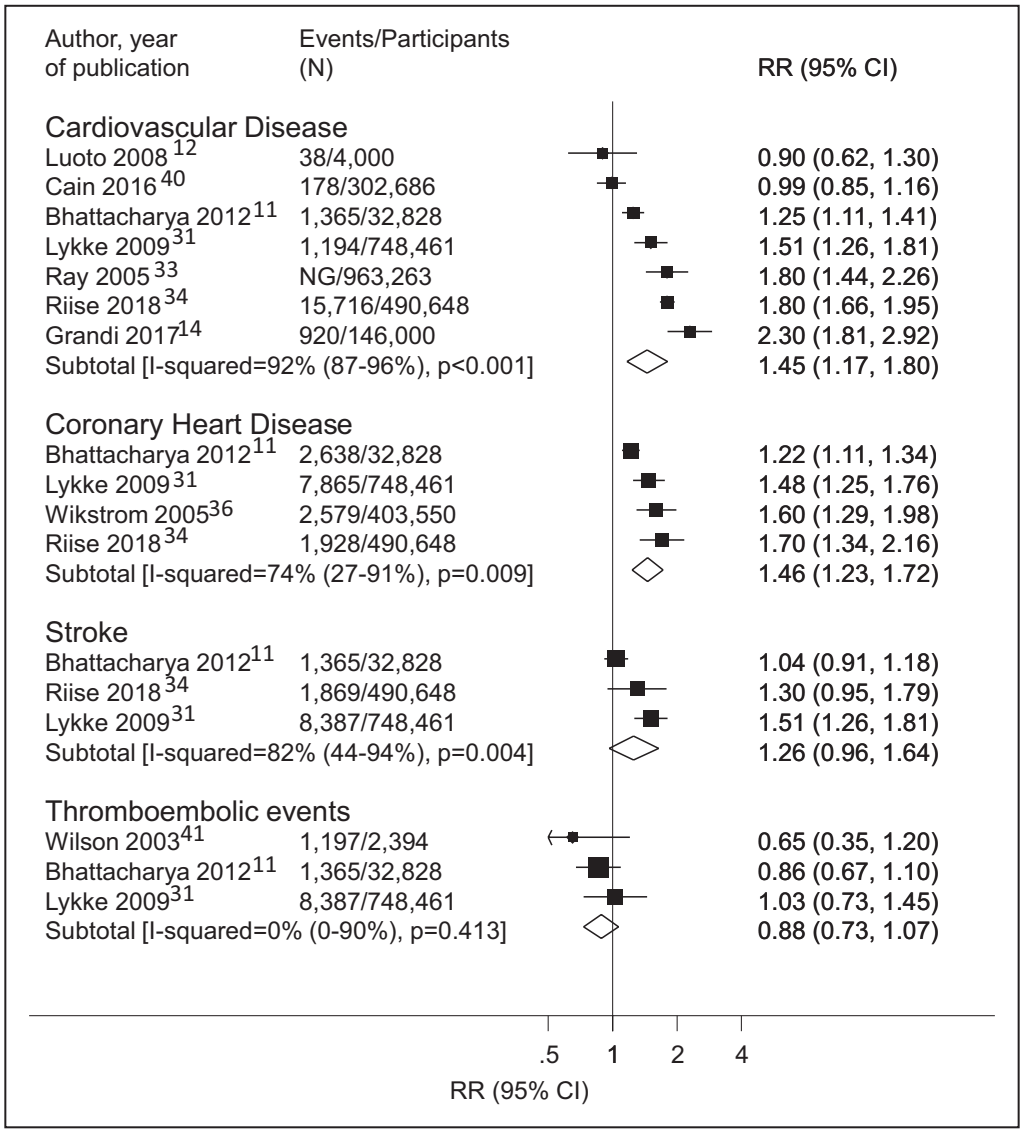


Figure 3. Association between gestational hypertension in a woman's first pregnancy and subsequent risk of cardiovascular events in adjusted analyses.
RR indicates relative risk.

meta-analysis, there was evidence for a greater risk of any stroke outcome for women with 1 or more pregnancies affected by GH: RR, 1.96 (95% CI, 1.06–3.63). Evidence for between-study heterogeneity was found in this analysis (98%, $P<0.001$) (Figure S3).

The overall CVD analyses were separately stratified by average duration of follow-up, risk of bias, level of adjustment, year of publication, and population (Table S10). There was no evidence that risk estimates varied between strata, and there remained evidence of heterogeneity in most categories after stratification.

Small Study Effects

The funnel plot for overall CVD risk after GH in the first pregnancy did not show evidence of asymmetry (Egger test, $P=0.935$) (Figure S4). The funnel plot for a history of GH and overall CVD risk indicated potential asymmetry ($P=0.051$), with publications of small studies with null or negative effect estimates missing (Figure S5). Use of the trim-and-fill method resulted in a RR of 1.26 (95% CI, 1.15–1.39). The funnel plot for a history of GH and risk of any stroke outcome did not show evidence of asymmetry ($P=0.382$) (Figure S6).

DISCUSSION

This systematic review found that women previously diagnosed with GH had a greater risk of overall CVD, CHD, and heart failure and some indication of a greater risk of stroke as well.

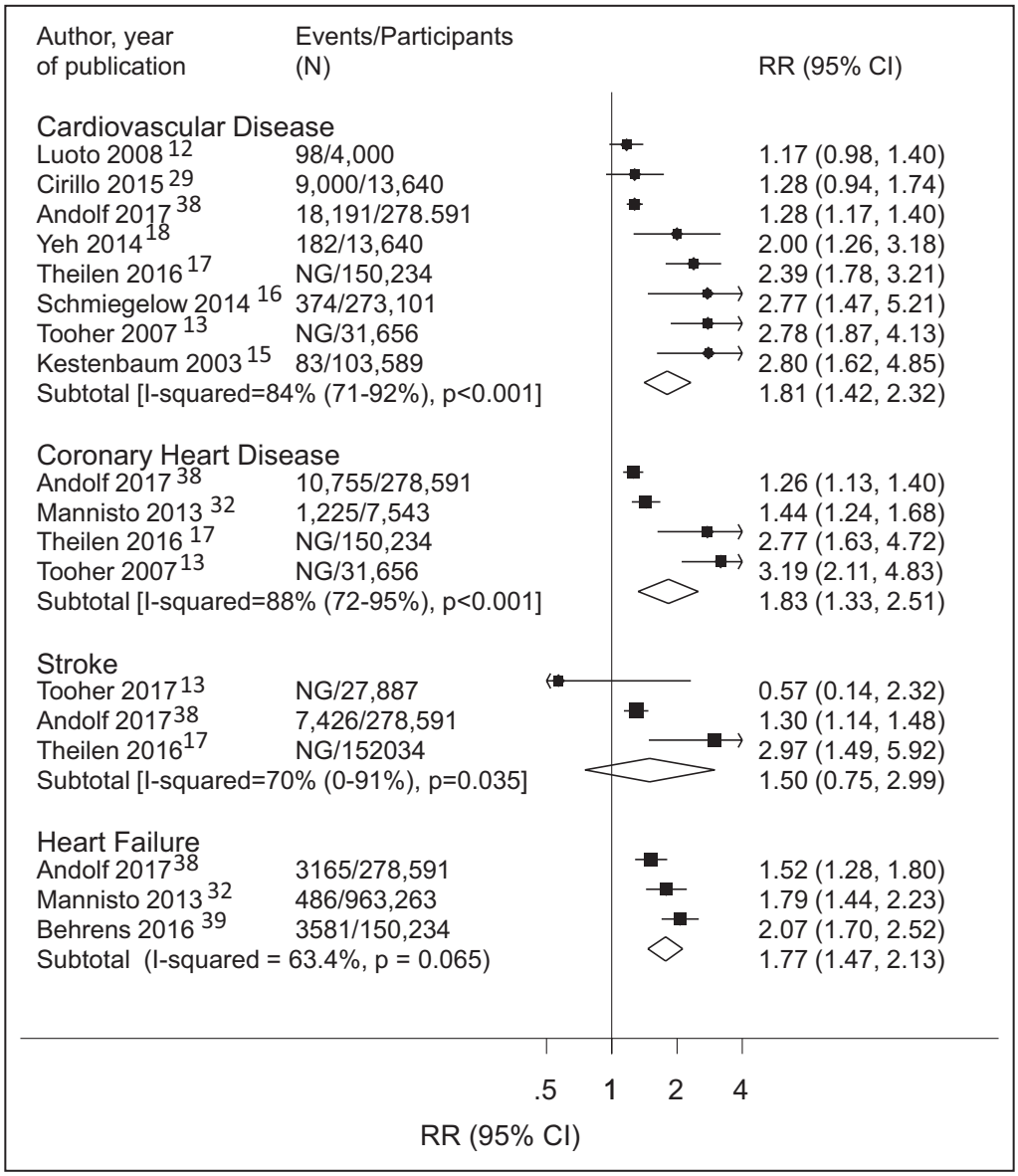


Figure 4. Association between a history of one or more pregnancies affected by gestational hypertension and subsequent risk of cardiovascular events in adjusted analyses.
NG indicates not given; and RR, relative risk.

This study adds to the literature on the relationship between women's obstetric history and risk of cardiovascular events. A single previous review evaluated cardiovascular events after GH[42]; however, they focused on morbidity from CVD and cerebrovascular disease only. Our findings substantially build on it providing a comprehensive, holistic review of the risk of fatal and nonfatal cardiovascular events after GH.

This study adds to the growing literature on the relationship between women's obstetric history and their subsequent risk of cardiovascular events. These include a greater risk of overall CVD with recurrent miscarriages,[43] preterm birth,[44] fetal growth restriction,[45] and pre-eclampsia.[46] The magnitude of association for overall CVD risk found in the current review is similar to that found with recurrent miscarriages,[43] preterm birth[44] and fetal growth restriction.[45] Although the overall CVD risk associated with pre-eclampsia is greater than that of GH.[46]

Strengths and Weaknesses of the Study

Strengths of this study include the large number of women included and the variety of cardiovascular events assessed, which allowed us to obtain the most holistic picture to date of the effect of GH on long-term cardiovascular health. Because of the larger number of studies included in the overall CVD analysis, it was possible to assess the impact of study characteristics

on the meta-analysis and to conduct sensitivity analyses. Furthermore, there was sufficient follow-up duration in many of the studies (10 studies had more than 15 years of follow-up) for long-term CVD risk to be adequately assessed. Lastly, diagnoses of GH and cardiovascular events were mainly ascertained through medical records, which reduced possible information bias arising from self-report.

Nevertheless, our study has limitations. First, it is possible that despite searching multiple databases without language or time restrictions, relevant studies were missed. Second, there were only 21 studies identified, and at most 8 studies were included in any single meta-analysis, suggesting that analyses could be influenced by a single study. However, exclusion of the studies with the largest effect estimates did not materially alter the conclusions of the meta-analyses. Few studies were found for some events, such as stroke and thromboembolic events, and thus limited sensitivity analyses.

Third, high heterogeneity (I^2>70%) was found for most meta-analyses. This may be attributed to differences in study design, methodology, or population. Stratified analyses in the current review were limited to CVD only and may have been underpowered to detect some of these differences. Other potential sources of heterogeneity include differences in the frequency of postpartum chronic hypertension and variation in outcome and exposure identification. Chronic hypertension is likely to be an important mediator of the relationship between GH and CVD,[40,47] therefore the frequency of conversion of GH to chronic hypertension may be a source of heterogeneity between populations and thus studies. Outcome definitions may have varied between studies because of the inclusion of different *International Classification of Diseases* (*ICD*) codes to define the same outcome (Table S4). Although all studies used robust measurements of exposure or events through blood pressure measurement and registries, revisions of *ICD* criteria could have led to differences in the definition of *ICD* codes between studies. Furthermore, there are challenges in identifying exposed women as well, as it requires a blood pressure measurement taken before 20 weeks gestation to rule out chronic hypertension, the criteria for which has changed over time, notably in the United States.[48]

Fourth, many studies were of poor quality, and there were different adjustment sets considered, which could have resulted in residual confounding. However, when low-quality studies were excluded, the results were broadly similar. Fifth, our funnel plot for overall CVD risk with a history of GH indicates some asymmetry where small studies that report a significant, positive result are more likely to be published (Figure S4). Use of the trim-and-fill method found that the association would remain after correcting for the asymmetry. Lastly, the majority of studies were from Western populations, which may limit the generalizability of these findings to other populations.

Implications for Clinical Practice

Several theories have been proposed to explain the link between GH and the development of CVD. Hypertension in pregnancy may cause lasting damage that contributes to CVD. Alternatively, or in addition to this, women who develop GH may have a pre-existing predisposition to CVD, which unmasks itself during pregnancy. For example, prepregnancy body mass index is particularly important for GH risk,[49] and body mass index, in general, is linked to CVD development.[50,51] These theories, in combination with the findings of this review, underscore the importance of intervention to decrease CVD risk factors. This could have the dual benefit of decreasing both the severity and incidence of GH and CVD.

The timing of when an intervention is administered merits discussion, and the pathological mechanisms linking GH to CVD development have implications for this. If there is a pre-existing predisposition to CVD, then intervention before conception should be a priority. There is increasing emphasis on the importance of preconception health and its implications for future health.[52] However, the challenges of intervening before conception lie in identifying women considering pregnancy and will not aid women with unplanned pregnancies, which may be up to half of all pregnancies in some groups of women.[53]

Intervention during or shortly after pregnancy may be a viable approach and may help mitigate any long-term damage caused by GH. Strategies for managing cardiovascular risk factors during pregnancy could include lifestyle changes that limit excess gestational weight gain, a known risk factor for GH and other pregnancy complications.[54,55] There is evidence that lifestyle changes can be effective in mitigating maternal and fetal risks,[56] and research is underway to identify the ideal interventions.[57] Women who experience GH may also benefit from counseling during and/or after pregnancy about their long-term cardiovascular risk. Strategies that could be implemented after pregnancy may include discussion of heart age calculations,[58,59] which may be more applicable to a younger population of women than predicting their cardiovascular risk, which is likely to be low in the years after giving birth.

Unanswered Questions and Future Research

Pre-eclampsia is currently recognized in guidelines for assessing CVD risk in women[9]; however, GH is not. To assess whether GH should also be included in CVD risk guidelines, further research is needed.

The risk of some diseases that have been evaluated in relation to GH, such as stroke subtypes, would benefit from further study to confirm the association indicated in this review, whereas many cardiovascular events have been entirely overlooked, such as peripheral arterial disease and transient ischemic attack. Furthermore, only 2 studies were identified that assessed a dose–response relationship, that is, whether the risk of a cardiovascular outcome rises with an increasing number of pregnancies affected by GH. Given the evidence for a dose–response relationship for both preterm birth and pre-eclampsia, whereby CVD risk is greater with the number of affected pregnancies,[60,61] the limited evaluation of a dose–response relationship for GH needs addressing.

CONCLUSIONS

In conclusion, we found that GH is associated with a greater risk of overall CVD, specifically CHD and heart failure. The greater risk associated with many of these events is similar to other pregnancy complications, such as preterm birth and fetal growth restriction. Women who experience GH should be aware of this greater risk and may benefit from prenatal and postnatal counseling to increase their awareness of strategies that can reduce their CVD risk during and after birth.

ARTICLE INFORMATION

Received July 19, 2019; accepted May 13, 2020.

Affiliations

From the Faculty of Health and Medicine, University of Newcastle, New South Wales, Australia (C.C.W.L.); Liverpool Hospital, Liverpool, New South Wales, Australia (C.C.W.L.); Department of Public Health and Primary Care & Cambridge Institute of Public Health (Strangeways Research Laboratory) (C.C.W.L.); Homerton College (A.C.Q.L., S.H.L., B.C., O.B., B.M., M.C., C.O.-W.) and Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care (C.O.-W.), University of Cambridge, United Kingdom; Hills Road Sixth Form College, Cambridge, United Kingdom (G.F.); Department of Obstetrics & Gynecology, School of Medicine, University of North Carolina, Chapel Hill, NC (C.J.V.); Population Health Sciences, Bristol Medical School, University of Bristol, United Kingdom (A.F.).

Acknowledgments

C.C.W.L, A.F.Q.L., S.H.L., G.F., B.C., O.B., B.M., M.C., C.J.V., A.F., and C.O.-W. were involved in designing the study. A.C.Q.L., S.H.L., G.F., B.C., O.B., B.M., M.C., and C.O.-W. were involved in searching the database. C.C.W.L., A.C.Q.L., S.H.L., G.F., B.C., O.B., B.M., and M.C. screened citations for inclusion. C.C.W.L., A.C.Q.L., S.H.L., and C.O.-W. were involved in risk-of-bias analysis. C.C.W.L., A.C.Q.L., and C.O.-W. were involved in extracting data and interpretation. C.O.-W. analyzed the data. C.C.W.L., A.C.Q.L., C.J.V., A.F., and C.O.-W. drafted the manuscript.

Sources of Funding

C.O.-W. was supported by the British Heart Foundation Cambridge Centre of Excellence (RE/13/6/30180) and an early career fellowship from Homerton College, University of Cambridge. A.F. is supported by a UK Medical Research Council Fellowship (MR/M009351/1). The funding source had no role in the design or conduct of the study, collection or analysis of the data, or the decision to submit the manuscript for publication.

Disclosures

None.

Supplementary Materials

Tables S1–S10
Figures S1–S6
References 11–18, and 29–41

REFERENCES

1. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstet Gynecol*. 2003;102:181–192.
2. American College of Obstetricians and Gynecologists. Practice Bulletin No. 202. *Obstet Gynecol*. 2019;133:e1–e25.
3. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987–2004. *Am J Hypertens*. 2008;21:521–526.
4. Roberts CL, Ford JB, Algert CS, Antonsen S, Chalmers J, Cnattingius S, Gokhale M, Kotelchuck M, Melve KK, Langridge A, et al. Population-based trends in pregnancy hypertension and pre-eclampsia: an international comparative study. *BMJ Open*. 2011;1:e000101.
5. Garovic VD, Hayman SR. Hypertension in pregnancy: an emerging risk factor for cardiovascular disease. *Nat Clin Pract Nephrol*. 2007;3:613–622.
6. Bellamy L, Casas J-P, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335:974.
7. Brown MC, Best KE, Pearce MS, Waugh J, Robson SC, Bell R. Cardiovascular disease risk in women with pre-eclampsia: systematic review and meta-analysis. *Eur J Epidemiol*. 2013;28:1–19.
8. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J*. 2008;156:918–930.
9. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VL, Shaw LJ, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women-2011 update: a guideline from the American Heart Association. *Circulation*. 2011;123:1243–1262.
10. *British Medical Journal*. BMJ Best Practice. Gestational hypertension. Available at: https://bestpractice.bmj.com/topics/en-gb/663. Accessed May 24, 2019.
11. Bhattacharya S, Prescott GJ, Iversen L, Campbell DM, Smith WCS, Hannaford PC. Hypertensive disorders of pregnancy and future health and mortality: a record linkage study. *Pregnancy Hypertens*. 2012;2:1–7.
12. Luoto R, Kharazmi E, Whitley E, Raitanen J, Gissler M, Hemminki E. Systolic hypertension in pregnancy and cardiovascular mortality: a 44-year follow-up study. *Hypertens pregnancy*. 2008;27:87–94.
13. Tooher J, Thornton C, Makris A, Ogle R, Korda A, Hennessy A. All hypertensive disorders of pregnancy increase the risk of future cardiovascular disease. *Hypertension*. 2017;70:798–803.
14. Grandi SM, Vallée-Pouliot K, Reynier P, Eberg M, Platt RW, Arel R, Basso O, Filion KB. Hypertensive disorders in pregnancy and the risk of subsequent cardiovascular disease. *Paediatr Perinat Epidemiol*. 2017;31:412–421.
15. Kestenbaum B, Seliger SL, Easterling TR, Gillen DL, Critchlow CW, Stehman-Breen CO, Schwartz SM. Cardiovascular and thromboembolic events following hypertensive pregnancy. *Am J Kidney Dis*. 2003;42:982–989.
16. Schmiegelow MD, Andersson C, Køber L, Andersen SS, Olesen JB, Jensen TB, Azimi A, Nielsen MB, Gislason G, Torp-Pedersen C. Prepregnancy obesity and associations with stroke and myocardial infarction in women in the years after childbirth: a nationwide cohort study. *Circulation*. 2014;129:330–337.
17. Theilen LH, Fraser A, Hollingshaus MS, Schliep KC, Varner MW, Smith KR, Esplin MS. All-cause and cause-specific mortality after hypertensive disease of pregnancy. *Obstet Gynecol*. 2016;128:238–244.
18. Yeh JS, Cheng H, Hsu P, Sung S, Liu W, Fang H, Chuang S. Synergistic effect of gestational hypertension and postpartum incident hypertension on cardiovascular health: a nationwide population study. *J Am Heart Assoc*. 2014;3:e001008. DOI: 10.1161/JAHA.114.001008.

19. The National Institute for Health and Care Excellence. 4-year surveillance review of CG107: hypertension in pregnancy: the management of hypertensive disorders during pregnancy. Available at: https://www.nice.org.uk/guidance/cg107/documents/cg107-hypertension-in-pregnancy-review-proposal2. Accessed May 24, 2019.
20. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008–2012.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
22. Booth A, Clarke M, Ghersi D, Moher D, Petticrew M, Stewart L. An international registry of systematic-review protocols. *Lancet*. 2011;377:108–109.
23. Wallace BC, Small K, Brodley CE, Lau J, Trikalinos TA. Deploying an interactive machine learning system in an evidence-based practice center. In: IHI 12 Conference Committee. (eds). Proceedings of the 2nd ACM SIGHIT Symposium on International Health Informatics–IHI '12. New York, New York: ACM Press; 2012:819.
24. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25:603–605.
25. Wilkins E, Wilson L, Wickramasinghe K, Bhatnagar P, Leal J, Luengo-Fernandez R, Burns R, Rayner M, Townsend N. European cardiovascular disease statistics 2017. Available at: http://www.ehnheart.org/cvd-statistics.html. Accessed May 24, 2019.
26. Cornell JE, Mulrow CD, Localio R, Stack CB, Meibohm AR, Guallar E, Goodman SN. Random-effects meta-analysis of inconsistent effects: a time for change. *Ann Intern Med*. 2014;160:267–270.
27. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
28. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455–463.
29. Andolf EG, Sydsjö GCM, Bladh MK, Berg G, Sharma S. Hypertensive disorders in pregnancy and later dementia: a Swedish National Register Study. *Acta Obstet Gynecol Scand*. 2017;96:464–471.
30. Behrens I, Basit S, Lykke JA, Ranthe MF, Wohlfahrt J, Bundgaard H, Melbye M, Boyd HA. Association between hypertensive disorders of pregnancy and later risk of cardiomyopathy. *JAMA*. 2016;315:1026–1033.
31. Cain MA, Salemi JL, Tanner JP, Kirby RS, Salihu HM, Louis JM. Pregnancy as a window to future health: maternal placental syndromes and short-term cardiovascular outcomes. *Am J Obstet Gynecol*. 2016;215:484.e1–484.e14.
32. Cirillo PM, Cohn BA. Pregnancy complications and cardiovascular disease death. *Circulation*. 2015;132:1234–1242.
33. Lykke JA, Langhoff-Roos J, Lockwood CJ, Triche EW, Paidas MJ. Mortality of mothers from cardiovascular and non-cardiovascular causes following pregnancy complications in first delivery. *Paediatr Perinat Epidemiol*. 2010;24:323–330.
34. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension*. 2009;53:944–951.
35. Männistö T, Mendola P, Vääräsmäki M, Järvelin M-R, Hartikainen A-L, Pouta A, Suvanto E. Elevated blood pressure in pregnancy and subsequent chronic disease risk. *Circulation*. 2013;127:681–690.
36. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet*. 2005;366:1797–1803.
37. Riise HKR, Sulo G, Tell GS, Igland J, Nygård O, Iversen A-C, Daltveit AK. Association between gestational hypertension and risk of cardiovascular disease among 617 589 Norwegian women. *J Am Heart Assoc*. 2018;7:e008337. DOI: 10.1161/JAHA.117.008337.
38. Riise HKR, Sulo G, Tell GS, Igland J, Egeland G, Nygard O, Selmer R, Iversen A-C, Daltveit AK. Hypertensive pregnancy disorders increase the risk of maternal cardiovascular disease after adjustment for cardiovascular risk factors. *Int J Cardiol*. 2019;282:81–87.
39. Wikstrom A-K, Haglund B, Olovsson M, Lindeberg SN. The risk of maternal ischaemic heart disease after gestational hypertensive disease. *BJOG*. 2005;112:1486–1491.
40. Wilson BJ, Watson MS, Prescott GJ, Sunderland S, Campbell DM, Hannaford P, Smith WCS. Hypertensive diseases of pregnancy and risk of hypertension and stroke in later life: results from cohort study. *BMJ*. 2003;326:845.
41. Lin L-T, Tsui K-H, Cheng J-T, Cheng J-S, Huang W-C, Liou W-S, Tang P-L. Increased risk of intracranial hemorrhage in patients with pregnancy-induced hypertension: a nationwide population-based retrospective cohort study. *Medicine (Baltimore)*. 2016;95:e3732.
42. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, Smith GN, Gore GC, Ray JG, Nerenberg K, et al. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications. *Circulation*. 2019;139:1069–1079.
43. Oliver-Williams CT, Heydon EE, Smith GCS, Wood AM. Miscarriage and future maternal cardiovascular disease: a systematic review and meta-analysis. *Heart*. 2013;99:1636–1644.
44. Wu P, Gulati M, Kwok CS, Wong CW, Narain A, O'Brien S, Chew-Graham CA, Verma G, Kadam UT, Mamas MA. Preterm delivery and future risk of maternal cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2018;7:e007809. DOI: 10.1161/JAHA.117.007809.
45. Bukowski R, Davis KE, Wilson PWF. Delivery of a small for gestational age infant and greater maternal risk of ischemic heart disease. *PLoS One*. 2012;7:e33047.
46. Wu P, Haththotuwa R, Kwok CS, Babu A, Kotronias RA, Rushton C, Zaman A, Fryer AA, Kadam U, Chew-Graham CA, et al. Preeclampsia and future cardiovascular health. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003497. DOI: 10.1161/CIRCOUTCOMES.116.003497.
47. Timpka S, Stuart JJ, Tanz LJ, Rimm EB, Franks PW, Rich-Edwards JW. Lifestyle in progression from hypertensive disorders of pregnancy to chronic hypertension in Nurses' Health Study II: observational cohort study. *BMJ*. 2017;358:j3024.
48. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018;138:e426–e483.
49. Shin D, Song WO. Prepregnancy body mass index is an independent risk factor for gestational hypertension, gestational diabetes, preterm labor, and small- and large-for-gestational-age infants. *J Matern Fetal Neonatal Med*. 2015;28:1679–1686.
50. Chen Y, Copeland WK, Vedanthan R, Grant E, Lee JE, Gu D, Gupta PC, Ramadas K, Inoue M, Tsugane S, et al. Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium. *BMJ*. 2013;347:f5446.
51. Lyall DM, Celis-Morales C, Ward J, Iliodromiti S, Anderson JJ, Gill JMR, Smith DJ, Ntuk UE, Mackay DF, Holmes MV, et al. Association of body mass index with cardiometabolic disease in the UK Biobank: a Mendelian randomization study. *JAMA Cardiol*. 2017;2:882–889.
52. Stephenson J, Heslehurst N, Hall J, Schoenaker DAJM, Hutchinson J, Cade JE, Poston L, Barrett G, Crozier SR, Barker M, et al. Before the beginning: nutrition and lifestyle in the preconception period and its importance for future health. *Lancet*. 2018;391:1830–1841.
53. Finer LB, Zolna MR. Shifts in intended and unintended pregnancies in the United States, 2001–2008. *Am J Public Health*. 2014;104(suppl 1):S43–S48.
54. Macdonald-Wallis C, Tilling K, Fraser A, Nelson SM, Lawlor DA. Gestational weight gain as a risk factor for hypertensive disorders of pregnancy. *Am J Obstet Gynecol*. 2013;209:327.e1–327.e17.
55. Hedderson MM, Gunderson EP, Ferrara A. Gestational weight gain and risk of gestational diabetes mellitus. *Obstet Gynecol*. 2010;115:597–604.
56. Thangaratinam S, Rogozinska E, Jolly K, Glinkowski S, Roseboom T, Tomlinson JW, Kunz R, Mol BW, Coomarasamy A, Khan KS. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. *BMJ*. 2012;344:e2088.
57. Dodd JM, Grivell RM, Louise J, Deussen AR, Giles L, Mol BW, Vinter C, Tanvig M, Moller Jensen D, Bogaerts A, et al. The effects of dietary and lifestyle interventions among pregnant women who are overweight or obese on longer-term maternal and early childhood outcomes: protocol for an individual participant data (IPD) meta-analysis. *Syst Rev*. 2017;6:51.

58. Grover SA, Lowensteyn I, Joseph L, Kaouache M, Marchand S, Coupal L, Boudreau G; Cardiovascular Health Evaluation to Improve Compliance and Knowledge Among Uninformed Patients (CHECK-UP) Study Group. Patient knowledge of coronary risk profile improves the effectiveness of dyslipidemia therapy: the CHECK-UP study: a randomized controlled trial. *Arch Intern Med*. 2007;167: 2296–2303.
59. Lopez-Gonzalez AA, Aguilo A, Frontera M, Bennasar-Veny M, Campos I, Vicente-Herrero T, Tomas-Salva M, De Pedro-Gomez J, Tauler P. Effectiveness of the Heart Age tool for improving modifiable cardiovascular risk factors in a Southern European population: a randomized trial. *Eur J Prev Cardiol*. 2015;22:389–396.
60. Auger N, Fraser WD, Schnitzer M, Leduc L, Healy-Profitós J, Paradis G. Recurrent pre-eclampsia and subsequent cardiovascular risk. *Heart*. 2017;103:235–243.
61. Catov JM, Sen WuC, Olsen J, Sutton-Tyrrell K, Li J, Nohr EA. Early or recurrent preterm birth and maternal cardiovascular disease risk. *Ann Epidemiol*. 2010;20:604–609.

Supplemental Material

Table S1. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3-4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4-5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5, 9-13, Tables S4, S5 & S7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Tables S6 & S10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table S8 & S9, Fig 3 & 4 Fig S1, S2 & S3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig 2, 3 & 4 Fig S1, S2 & S3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5, 7,Table S11, Fig S4, S5 & S6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7, Table S9 & S10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	7-9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

Table S2. MOOSE Checklist for Meta-analyses of Observational Studies.

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	3
2	Hypothesis statement	3
3	Description of study outcome(s)	3
4	Type of exposure or intervention used	3
5	Type of study designs used	3
6	Study population	3
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	4
8	Search strategy, including time period included in the synthesis and key words	3
9	Effort to include all available studies, including contact with authors	3
10	Databases and registries searched	3
11	Search software used, name and version, including special features used (eg, explosion)	3-4
12	Use of hand searching (eg, reference lists of obtained articles)	3
13	List of citations located and those excluded, including justification	Figure 1
14	Method of addressing articles published in languages other than English	None found
15	Method of handling abstracts and unpublished studies	None found
16	Description of any contact with authors	None required
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	4
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	4
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	4, Table S5
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	4, Table S4, TableS 9
22	Assessment of heterogeneity	4
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	4
24	Provision of appropriate tables and graphics	Fig 1, Tables S1-S7
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Fig 2-4, Fig S1,S2
26	Table giving descriptive information for each study included	Table S4,S5,S7

27	Results of sensitivity testing (eg, subgroup analysis)	7, Table S10-S11, Fig S3
28	Indication of statistical uncertainty of findings	Fig 2-4, Fig S1, S2
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	8, Fig S4-S6
30	Justification for exclusion (eg, exclusion of non-English language citations)	n/a
31	Assessment of quality of included studies	8, Table S6-S7
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	8-9
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	8
34	Guidelines for future research	9
35	Disclosure of funding source	1

Table S3. PubMed Search Strategy.

Population	("humans"[MeSH Terms] OR "Women"[Mesh] OR "Female"[Mesh] OR "Pregnancy"[Mesh]) AND
Exposure	("Hypertension, Pregnancy-Induced"[Mesh] OR “Gestational hypertension*”[All Fields] OR “Pregnancy Induced Hypertension*”[All Fields] OR “Transient Hypertension* in Pregnancy”[All Fields]) AND
Outcome	(“Acute Coronary Syndrome”[All Fields] OR “Aneurysm”[All Fields] OR “Angina”[All Fields] OR “Aortic Stenosis”[All Fields] OR “Aortic Stenoses”[All Fields] OR “Aortic Valve Insufficienc*”[All Fields] OR “Aortic Valve Stenosis”[All Fields] OR “Aortic Valve Stenoses”[All Fields] OR “Arrhythmia*”[All Fields] OR “Atrial Fibrillation*”[All Fields] OR “Atrial Flutter*”[All Fields] OR “Bradycardia”[All Fields] OR “Cardiac Arrest*”[All Fields] OR “Cardiac Oedema”[All Fields] OR “Cardiac edema”[All Fields] OR “Cardiac Tamponade”[All Fields] OR “Cardiomegal*”[All Fields] OR “Cardiomyopath*”[All Fields] OR “Cardiovascular Disease*”[All Fields] OR “CVD”[All Fields] OR “Cerebrovascular Disease*”[All Fields] OR “Cerebrovascular Disorder*”[All Fields] OR “Cerebral infarction*”[All Fields] OR “Cerebral haemorrhage*”[All Fields] OR “Cerebral hemorrhage*”[All Fields] OR “Commotio Cordis”[All Fields] OR “Coronary Artery Disease*”[All Fields] OR “Coronary Disease*”[All Fields] OR “CHD”[All Fields] OR “Coronary Occlusion*”[All Fields] OR “Coronary Restenosis”[All Fields] OR “Coronary Restenoses”[All Fields] OR “Coronary Stenosis”[All Fields] OR “Coronary Stenoses”[All Fields] OR “Coronary Vasospasm”[All Fields] OR “Emboli”[All Fields] OR “Embolism”[All Fields] OR “Endocarditis”[All Fields] OR “Heart Arrest*”[All Fields] OR “Heart Attack*”[All Fields] OR “Heart Block*”[All Fields] OR “Heart Disease*”[All Fields] OR “Heart Failure*”[All Fields] OR “Heart Rupture*”[All Fields] OR “Heart Valve Disease*”[All Fields] OR “Heart Valve Prolapse*”[All Fields] OR “Hypertroph*”[All Fields] OR “Intracranial Haemorrhage*”[All Fields] OR “Intracranial Hemorrhage*”[All Fields] OR “Long QT Syndrome”[All Fields] OR “Mitral Valve Insufficienc*”[All Fields] OR “Myocardial Infarction*”[All Fields] OR “Myocardial Ischemia”[All Fields] OR “Myocardial Ischaemia”[All Fields] OR “Myocardial Reperfusion Injury”[All Fields] OR “Myocardial Stunning”[All Fields] OR “Paroxysmal Dyspnea”[All Fields] OR “Peripheral arterial disease”[All Fields] OR “Pre-Excitation Syndrome”[All Fields] OR “Pulmonary Valve Insufficiency”[All Fields] OR “Pulmonary Valve Stenosis”[All Fields] OR “Pulmonary Valve Stenoses”[All Fields] OR “Pulmonary Heart Disease”[All Fields] OR “Stroke”[All Fields] OR “Sudden Cardiac”[All Fields] OR “Subarachnoid haemorrhage”[All Fields] OR “Subarachnoid hemorrhage”[All Fields] OR “Tachycardia”[All Fields] OR “Thrombosis”[All Fields] OR “Thromboses”[All Fields] OR “Transient Ischaemic Attack”[All Fields] OR “Transient Ischemic Attack”[All Fields] OR “Tricuspid Valve Insufficiency”[All Fields] OR “Tricuspid Valve Stenosis”[All Fields] OR “Tricuspid Valve Stenoses”[All Fields] OR “Ventricular Dysfunction”[All Fields] OR “Ventricular Fibrillation”[All Fields] OR “Ventricular Flutter”[All Fields] OR "Acute Coronary Syndrome"[Mesh] OR "Aneurysm"[Mesh] OR "Angina Pectoris"[Mesh] OR "Aortic Valve Stenosis"[Mesh] OR "Aortic Valve Insufficiency"[Mesh] OR "Arrhythmias, Cardiac"[Mesh] OR "Atrial Fibrillation"[Mesh] OR "Atrial Flutter"[Mesh] OR "Bradycardia"[Mesh] OR "Heart Arrest"[Mesh] OR "Edema, Cardiac"[Mesh] OR "Cardiac Tamponade"[Mesh] OR "Cardiomegaly"[Mesh] OR "Cardiomyopathies"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR "Cerebrovascular Disorders"[Mesh] OR "Commotio Cordis"[Mesh]) OR "Coronary Artery Disease"[Mesh] OR "Coronary Disease"[Mesh] OR "Coronary Occlusion"[Mesh] OR "Coronary Restenosis"[Mesh] OR "Coronary Stenosis"[Mesh] OR "Coronary Vasospasm"[Mesh] OR "Embolism"[Mesh] OR "Endocarditis"[Mesh] OR "Myocardial Infarction"[Mesh] OR "Heart Block"[Mesh] OR "Heart Diseases"[Mesh] OR "Heart Failure"[Mesh] OR "Heart Rupture"[Mesh] OR "Heart Valve Diseases"[Mesh] OR "Heart Valve Prolapse"[Mesh] OR "Hypertrophy"[Mesh] OR "Intracranial Hemorrhages"[Mesh] OR "Long QT Syndrome"[Mesh] OR "Mitral Valve Insufficiency"[Mesh] OR "Myocardial Ischemia"[Mesh] OR "Myocardial Reperfusion Injury"[Mesh] OR "Myocardial Stunning"[Mesh] OR "Dyspnea, Paroxysmal"[Mesh] OR "Peripheral Arterial Disease"[Mesh] OR "Pre-Excitation Syndromes"[Mesh] OR "Pulmonary Valve Insufficiency"[Mesh] OR "Pulmonary Valve Stenosis"[Mesh] OR "Pulmonary Heart Disease"[Mesh] OR "Stroke"[Mesh] OR "Death, Sudden, Cardiac"[Mesh] OR "Subarachnoid Hemorrhage"[Mesh] OR "Tachycardia"[Mesh] OR "Thrombosis"[Mesh] OR "Ischemic Attack, Transient"[Mesh] OR "Tricuspid Valve Insufficiency"[Mesh] OR "Tricuspid Valve Stenosis"[Mesh] OR "Ventricular Dysfunction"[Mesh] OR "Ventricular Fibrillation"[Mesh] OR "Ventricular Flutter"[Mesh]) AND
Study Design	(“longitudinal studies"[MeSH Terms] OR “longitudinal study”[All Fields] OR “longitudinal studies”[All Fields] OR "prospective"[All Fields] OR “cohort”[All Fields] OR “cohorts”[All Fields] OR “follow up”[All Fields] OR “follow-up”[All Fields] OR "Epidemiology"[Mesh] OR "Epidemiology"[All Fields] OR "Epidemiological"[All Fields] OR "Retrospective Studies"[Mesh] OR "Retrospective"[All Fields] OR “prospective”[All Fields] OR "Cross-Sectional Studies"[Mesh] OR "Cross-Sectional"[All fields] OR "Cross Sectional"[All fields] OR "Case-Control Studies"[Mesh] OR "Case-Control"[All Fields])

Table S4. Definitions of Cardiovascular Events.

First author, year	Definition
Andolf et al. 2017[30]	Coronary Heart Disease: ICD-10 (I20-25) Stroke: ICD-10 (I60-69) Heart Failure: ICD-10 (I50)
Behrens et al. 2016[31]	Congestive Heart Failure: ICD-8 (427.09-427.19, 427.99, 428.99, 782.49); ICD-10 (I50.0-50.9); Cardiomyopathy: ICD-8 (425.99); ICD-10 (I42.0-43.8, O90.3)
Bhattacharya et al. 2012[11]	CHD: ICD-9 (410-4, 428); ICD-10 (I20-5, I50); Stroke: ICD-9 (430-8); ICD-10 (I60-9); CVD: ICD-9 (390-459); ICD-10 (I00-I99, G45)
Cain et al. 2016[32]	CVD: ICD-9 codes for CHD, cerebrovascular disease, peripheral artery disease, or congestive heart failure, or for cardiac or peripheral arterial revascularization that were not specified
Cirillo et al. 2015[33]	CVD mortality: ICD-7 (420.1); ICD-8 (410, 412); ICD-9 (410, 411, 414, 429), ICD-10 (I21, I24, I25)
Grandi et al. 2017[14]	CVD: Read codes for cerebrovascular disease, CHD, coronary revascularization, MI, peripheral arterial disease, transient ischaemic attack and stroke
Kestenbaum et al. 2003[15]	Thromboembolism: ICD-9 (451.1, 453, 415.1); CVD: ICD-9 (410, 430, 431, 434, 436), coronary artery revascularization procedure, including coronary artery bypass grafting (procedure code:36)
Lin et al. 2016[29]	Intracerebral haemorrhage: ICD-9 (430–432)
Luoto et al. 2008[12]	CVD: ICD-9 (389-459); ICD-10 (I00-I99)
Lykke et al. 2009[35]	CHD: ICD-8 (410-414), ICD-10 (I20-I25); Heart Failure: ICD-8 (42709-42711, 42719, 42799, 42899, 42900, 42908, 42909), ICD-10 (I50, I51.3, I51.9) Thromboembolic event: ICD-8 (444, 450-1), ICD-10 (I26, I74, I82) Stroke: ICD-8 (430-438), ICD-10 (I60-I67, G45)
Lykke et al. 2010[34]	CVD: ICD-8 (39-44, 451-458), ICD-10 (DI0-DI9)
Männistö et al. 2013[36]	CHD, MI, Heart failure, Ischemic stroke: ICD codes, which were not specified
Ray et al. 2005[37]	CVD: ICD-9, ICD-10 codes, which were not specified
Riise et al. 2018[38]	CVD: ICD-9 (390–459); ICD-10 (I00–I99, except I84); CHD: ICD-9 (410–414); ICD-10 (I20–I25); Stroke: ICD-9 (430–438); ICD-10 (I60–I69)
Riise et al. 2019[39]	Acute MI or acute cerebral stroke - composite of hospitalization with AMI: ICD-9 (410); ICD-10 (I21-22); death from CHD: ICD-9 (410-414), ICD-10 (I20-25); hospitalization or death with acute cerebral stroke: ICD-9 (43), ICD-10 (I60-61, I63-64, except I63.6)

Schmiegelow et al. 2014[16]	MI: ICD-10 (I21-I22); CVD: ICD-10 (I00-I99); Ischemic stroke: ICD-10 (I63-I64).
Theilen et al. 2016[17]	CVD: ICD-9 (390–459); CHD, Stroke: Codes not specified
Tooher et al. 2017[13]	CHD, Stroke: ICD-9 & ICD-10 codes, which weren't specified
Wikstrom et al. 2005[40]	CHD: ICD-9 (410–414), ICD-10 (I20–I25)
Wilson et al 2003[41]	Angina, MI, DVT: ascertained through the women's general practitioner, medical and death records Other circulatory disease: ICD-9 (390-8, 405, 415-27, 440-59), ICD-10 (I00-9, I15, I26-8, I30-49, I51-2, I70-99)
Yeh et al. 2014[18]	CVD, ICD-9 (390-459)

CHD – coronary heart disease; CVD – cardiovascular disease; ICD – International classification of diseases; MI – myocardial infarction

Table S5. Risk of Bias Assessment in Prospective Studies.

First author, year	Selection	Comparability	Outcome	Overall Assessment
Andolf et al. 2017 [30]	★★★	★★	★★	Low Risk of Bias
Behrens et al. 2016[31]	★★★★	★★	★★★	Low Risk of Bias
Bhattacharya et al. 2012[11]	★★★	★★	★★	Low Risk of Bias
Cain et al. 2016[32]	★★★★	★★	★★	Low Risk of Bias
Cirillo et al. 2015[33]	★★★★	★★	★★★	Low Risk of Bias
Grandi et al. 2017[14]	★★★★	★★	★	High Risk of Bias
Kestenbaum et al. 2003 [15]	★★★★	★★	★	High Risk of Bias
Lin et al. 2016[29]	★★★★	★	★	High Risk of Bias
Luoto et al. 2008[12]	★★	★★	★ ★	Moderate Risk of Bias
Lykke et al. 2009[35]	★★★★	★★	★★	Low Risk of Bias
Lykke et al. 2010[34]	★★★★	★★	★★	Low Risk of Bias
Männistö et al. 2013[36]	★★★	★★	★★	Low Risk of Bias
Ray et al. 2005[37]	★★★★	★★	★★	Low Risk of Bias
Riise et al. 2018[38]	★★★★	★★	★★★	Low Risk of Bias
Riise et al. 2019[39]	★★★★	★★	★★★	Low Risk of Bias
Schmiegelow et al. 2014[16]	★★★★	★★	★★	Low Risk of Bias
Theilen et al. 2016[17]	★★★★	★★	★	High Risk of Bias
Tooher et al. 2017[13]	★★★	★★	★	High Risk of Bias
Wikstrom et al. 2005[40]	★★★★	★★	★★	Low Risk of Bias
Wilson et al. 2003[41]	★★★	★★	★★	Low Risk of Bias
Yeh et al. 2014[18]	★★★★	★	★★	Low Risk of Bias

Acceptable loss of follow-up taken to be <10%; Sufficient duration of follow-up taken to be from average age at pregnancy to after menopause (52 years old)

Table S6. Adjustments of Included Studies.

First author, year	Adjustment factors	Quality of adjustment
Andolf et al. 2017[30]	Mother's age at birth, mother's attained educational level in 1985, marital status and origin (Nordic/non-Nordic), history of cardiovascular disease later in life (diabetes, arteriosclerosis, stroke, ischemic heart disease, heart failure and hypertension)	Adequate
Behrens et al. 2016[31]	Maternal age, maternal birth year, parity, multiple pregnancy and stillbirth	Poor
Bhattacharya et al. 2012[11]	Year of birth, social class and smoking	Poor
Cain et al. 2016[32]	Age, race/ethnicity, nativity, education, income, 5-year history of hyperlipidemia, migraine, lupus; pre-pregnancy BMI, gestational diabetes, tobacco use, drug use, and infant sex	Well
Cirillo et al. 2015[33]	Age, race, parity, BMI, and cigarette smoking	Well
Grandi et al. 2017[14]	Age, smoking, BMI, excessive alcohol use, year of cohort entry, region of residence, multiple gestation at first pregnancy, depression, dyslipidaemia, venous thromboembolism, polycystic ovary syndrome, gestational diabetes (measured between 12 weeks of gestation and 6 weeks post-partum), diabetes mellitus, renal disease, migraines, family history of hypertension and family history of cardiovascular disease any time before cohort entry, number of distinct drug classes prescribed, and use of statin, aspirin and anti-depressant medications in the year prior to pregnancy	Well
Kestenbaum et al. 2003[15]	Age, parity, calendar year of delivery	Poor
Lin et al. 2016[29]	Age, follow-up years	Poor
Luoto et al. 2008[12]	Age, hormone use, height, marital status and visit to private doctor	Adequate
Lykke et al. 2009[35]	Age, year of delivery, preterm delivery, SGA offspring, placental abruption, stillbirth and later type 2 diabetes mellitus	Adequate
Lykke et al. 2010[34]	Age, year of delivery.	Poor
Männistö et al. 2013[36]	Age at pregnancy, pre-pregnancy BMI, smoking, parity, diabetes mellitus before/during pregnancy, socioeconomic status	Well
Ray et al. 2005[37]	Age, multiple gestation, length of stay, income quintile, rural residence, drug dependence, and gestational diabetes mellitus in index delivery, and hypertension, any diabetes mellitus, obesity, dyslipidaemia, tobacco use, renal disease, migraine headache, and systemic lupus erythematosus	Well
Riise et al. 2018[38]	Age, educational level, marital status, and birth year of first child	Poor
Riise et al. 2019[39]	Age at recruitment age at first delivery, education (primary, high school/vocational, any college/ university) and a family history of MI prior to age 60	Well
Schmiegelow et al. 2014[16]	Age, smoking, and year of inclusion	Poor
Theilen et al. 2016[17]	Age, year of childbirth, parity, infant sex, parental education, preterm delivery, race-ethnicity, maternal marital status	Adequate
Tooher et al. 2017[13]	Age, gestation, and parity	Poor

Wikstrom et al. 2005[40]	Age, socio-economic level and category of hospital	Poor
Wilson et al. 2003[41] *	Age, BMI, social class, and smoking habit.	Adequate
Yeh et al. 2014[18]	Age, diabetes, dyslipidemia, incident hypertension, date of delivery	Poor

* Risk estimates for “other circulatory disease” were adjusted for age at delivery and social class only, and is considered poorly adjusted

Table S7. Results of Studies Included in the Meta-analysis by Outcome.

Outcome	First author, year	Exposure definition	Cases (N)	Point Estimate	Unadjusted or Age-adjusted Results	Adjusted Results *
Cardiovascular Disease	Bhattacharya et al. 2012[11]	GH in 1st pregnancy	1,319	IRR	1.19 (1.06,1.34)	1.25 (1.11,1.41)
	Cain et al. 2016[32]	GH in 1st pregnancy	2447	HR	1.18 (1.01, 1.37)	0.99 (0.85, 1.16)
	Grandi et al. 2017[14]	GH in 1st pregnancy	920 †	HR	2.4 (1.9, 3.1)	2.3 (1.8, 2.9)
	Luoto et al. 2008[12]	GH in 1st pregnancy	38	HR	0.87 (0.61, 1.25)	0.90 (0.62, 1.30)
	Lykke et al. 2010[34]	GH in 1st pregnancy	1,194	HR	NG	2.47 (1.74, 3.52)
	Ray et al. 2005[37]	GH in 1st pregnancy	1,987	HR	NG	1.8 (1.4, 2.2)
	Riise et al. 2018[38]	GH in 1st pregnancy	19,869	HR	1.8 (1.7, 2.0)	1.8 (1.7, 2.0)
	Cirillo et al. 2015 ‡[33]	A history of GH	9,000 †	HR	African American: 1.70 (1.10, 2.65) non-African American: 0.90 (0.63,1.36)	African American: 1.8 (1.09, 2.82) non-African American: 1.0 (0.68, 1.52)
	Kestenbaum et al. 2003[15]	A history of GH	83	HR	2.9 (1.8, 4.9)	2.8 (1.6, 4.8)
	Luoto et al. 2008[12] *	A history of GH	98	HR	1.18 (0.99, 1.40)	1.17 (0.98, 1.41)
	Schmiegelow et al. 2014[16]	A history of GH	374	HR	NG	2.77 (1.47, 5.21)
	Theilen et al. 2016[17]	A history of GH	NG	HR	NG	2.39 (1.78, 3.21)
	Yeh et al. 2014[18]	A history of GH	182	HR	NG	2.00 (1.26, 3.18)
Coronary Heart Disease	Bhattacharya et al. 2012[11]	GH in 1st pregnancy	681	IRR	1.09 (1.00,1.19)	1.22 (1.11, 1.34)
	Lykke et al.2009[35]	GH in 1st pregnancy	2,271	HR	1.67 (1.41, 1.97)	1.48 (1.25, 1.76)
	Riise et al. 2018[38]	GH in 1st pregnancy	2,364	HR	1.7 (1.3, 2.2)	1.7 (1.3, 2.1)
	Wikstrom et al. 2005[40]	GH in 1st pregnancy	2,142	IRR	2.0 (1.7, 2.5)	1.6 (1.3, 2.0)
	Andolf et al. 2017 [30] §	A history of GH	10,755 †	HR	1.33 (1.20, 1.48)	1.26 (1.13, 1.40)
	Männistö et al. 2013[36]	A history of GH	1,225	HR	NG	1.44 (1.24, 1.68)
	Tooher et al. 2017[13] §	A history of GH	NG	OR	NG	3.19 (2.11, 4.83)
	Theilen et al. 2016[17]	A history of GH	NG	HR	NG	2.77 (1.62, 4.75)
Stroke ‖	Bhattacharya et al. 2012[11]	GH in 1st pregnancy	2,638	IRR	0.97 (0.86,1.09)	1.04 (0.91,1.18)
	Lykke et al. 2009[35]	GH in 1st pregnancy	8,987	HR	1.68 (1.42, 1.97)	1.51 (1.26, 1.81)
	Riise et al. 2018[38]	GH in 1st pregnancy	2,452	HR	1.3 (0.9, 1.7)	1.3 (0.9, 1.7)
	Andolf et al. 2017 [30] §	A history of GH	7,436 †	HR	1.36 (1.20, 1.55)	1.30 (1.14, 1.48)
	Tooher et al. 2017[13] §	A history of GH	NG	OR	NG	0.57 (0.14, 2.31)
	Theilen et al. 2016[17]	A history of GH	NG	HR	NG	2.97 (1.49, 5.92)
Heart Failure	Andolf et al. 2017 [30]	A history of GH	3,165 †	HR	1.62 (1.36, 1.93)	1.52 (1.28, 1.80)
	Männistö et al. 2013[36]	A history of GH	486	IRR	NG	1.79 (1.43, 2.21)
	Behrens et al. 2016[31]	A history of GH	3,581	HR	NG	2.07 (1.70, 2.52)

Thromboembolic events¶	Bhattacharya et al. 2012[11]	GH in 1st pregnancy	384	IRR	0.82 (0.65,1.04)	0.86 (0.67,1.09)
	Lykke et al. 2009[35]	GH in 1st pregnancy	3,881	HR	1.01 (0.72-1.40)	1.03 (0.73, 1.45)
	Wilson et al. 2003[41]	GH in 1st pregnancy	47	OR	NG	0.65 (0.35, 1.20)

GH – gestational hypertension; NG – not given; HR – Hazard Ratio, OR – Odds Ratio, IRR – incident rate ratio

* See Table S4 for adjustment; † estimated; ‡ Results were combined by fixed effect meta-analysis to provide an estimate of the CVD risk for the whole population.

§ CHD and stroke results for each paper were combined by fixed effect meta-analysis to provide an estimate of the risk of CVD. ‖ Studies that reported all-cause stroke only. ¶ Study specific outcomes were: Wilson – Deep Vein Thrombosis, Bhattacharya - Pulmonary Embolism; Lykke – Thromboembolic Events

Table S8. Results of Studies Not Included in the Meta-analysis by Outcome.

Outcome	First author, year	Exposure definition	Cases (N)	Point Estimate	Unadjusted Results	Adjusted Results *
Heart Failure	Lykke et al 2009[35]	GH in 1st pregnancy	7,483	HR	1.57 (1.12-2.20)	1.37 (0.98-1.93)
Angina	Wilson et al. 2003[41]	GH in 1st pregnancy	64	OR	NG	1.02 (0.58 to 1.81)
Acute MI and acute cerebral stroke	Riise et al. 2019[39]	GH in 1st pregnancy	134	HR	2.4 (1.1-5.5)	1.8 (0.8-4.1)
Other circulatory disease †	Wilson et al. 2003[41]	GH in 1st pregnancy	172	IRR	NG	1.51 (1.06-2.14)
Myocardial Infarction	Wilson et al. 2003[41]	GH in 1st pregnancy	30	OR	NG	0.73 (0.32-1.63)
	Männistö et al. 2013[36]	A history of GH	471	IRR	NG	1.75 (1.40–2.19)
	Schmiegelow et al. 2014[16]	A history of GH	68	HR	NG	1.41 (0.19-10.21)
Intracerebral haemorrhage	Lin et al. 2016[29]	A history of GH	27	IRR	NG	3.72 (3.63-3.81)
Ischaemic Stroke	Männistö et al. 2013[36]	A history of GH	384	IRR	NG	1.59 (1.24-2.04)
	Schmiegelow et al. 2014[16]	A history of GH	175	HR	NG	2.78 (1.13-6.82)
Cardiomyopathy	Behrens et al. 2016[31]	A history of GH	1,448	HR	NG	1.83 (1.20-2.63)
Thromboembolic event	Kestenbaum et al. 2003[15]	A history of GH	127	HR	1.4 (0.8-2.4)	1.5 (0.9-2.5)
Cardiovascular Disease	Riise et al. 2018[38]	Pregnancies with GH in women with 2+ pregnancies	19,869	HR	NG	GH 1st pregnancy: 1.7 (1.5–2.0) GH 2nd pregnancy: 2.4 (2.1–2.8) 2+ GH pregnancies: 1.9 (1.8–2.0)
Coronary Heart Disease	Wikstrom et al. 2005[40]	Pregnancies with GH in women with 2+ pregnancies	1,242	IRR	GH 1st pregnancy: 1.9 (1.5-2.4) GH 2nd pregnancy: 2.7 (2.0–3.5) 2+ GH pregnancies: 3.3 (2.4–4.5)	GH 1st pregnancy: 1.9 (1.5-2.4) GH 2nd pregnancy: 2.4 (1.8–3.2) 2+ GH pregnancies 2.8 (2.0–3.9)

GH – gestational hypertension; MI – myocardial infarction; NG – not given; HR – Hazard Ratio, OR – Odds Ratio, IRR – incident rate ratio

* See Table S4 for adjustment. † Other circulatory disease excluding hypertension, cerebrovascular disease or coronary heart disease

Table S9. Sensitivity Analyses of Risk of Cardiovascular Events Estimated from the Adjusted Meta-Analyses.

Outcome	Exposure	Sensitivity Analysis	Excluded Studies	RR	(95% CI)	I^2	(95% CI)
Cardiovascular Disease	GH in 1st pregnancy	Excluding study(s) with the largest effect	Grandi 2017[14]	1.35	(1.08-1.69)	92%	(86-96%)
		Fixed effects model	n/a	1.52	(1.44-1.61)	92%	(87-96%)
	A history of GH	Excluding study(s) with the largest effect	Kestenbaum 2003[15]; Schmiegelow 2014[16]	1.65	(1.28-2.11)	76%	(46-89%)
		Fixed effects model	n/a	1.39	(1.29-1.49)	85%	(70-93%)
Coronary Heart Disease	GH in 1st pregnancy	Excluding study(s) with the largest effect	Riise 2018[38]	1.40	(1.17-1.66)	73%	(10-92%)
		Fixed effects model	n/a	1.35	(1.25-1.45)	74%	(27-91%)
	A history of GH	Excluding study(s) with the largest effect	Tooher et al. 2017[13]	1.49	(1.18-1.89)	78%	(31-93%)
		Fixed effects model	n/a	1.39	(1.28-1.52)	88%	(72-95%)
Stroke	GH in 1st pregnancy	Excluding study(s) with the largest effect	Not conducted *	-	-	-	-
		Fixed effects model	n/a	1.19	(1.06-1.32)	82%	(44-94%)
	A history of GH	Excluding study(s) with the largest effect	Not conducted *	-	-	-	-
		Fixed effects model	n/a	1.33	(1.17-1.51)	70%	(0-91%)
Heart Failure	A history of GH	Excluding study(s) with the largest effect	Not conducted *	-	-	-	-
		Fixed effects model	n/a	1.75	(1.57-1.95)	63%	(0-90%)

CI – Confidence Intervals; GH – Gestational Hypertension; RR – Relative Risk

* Fewer than four studies included in meta-analysis, so sensitivity analysis was not conducted

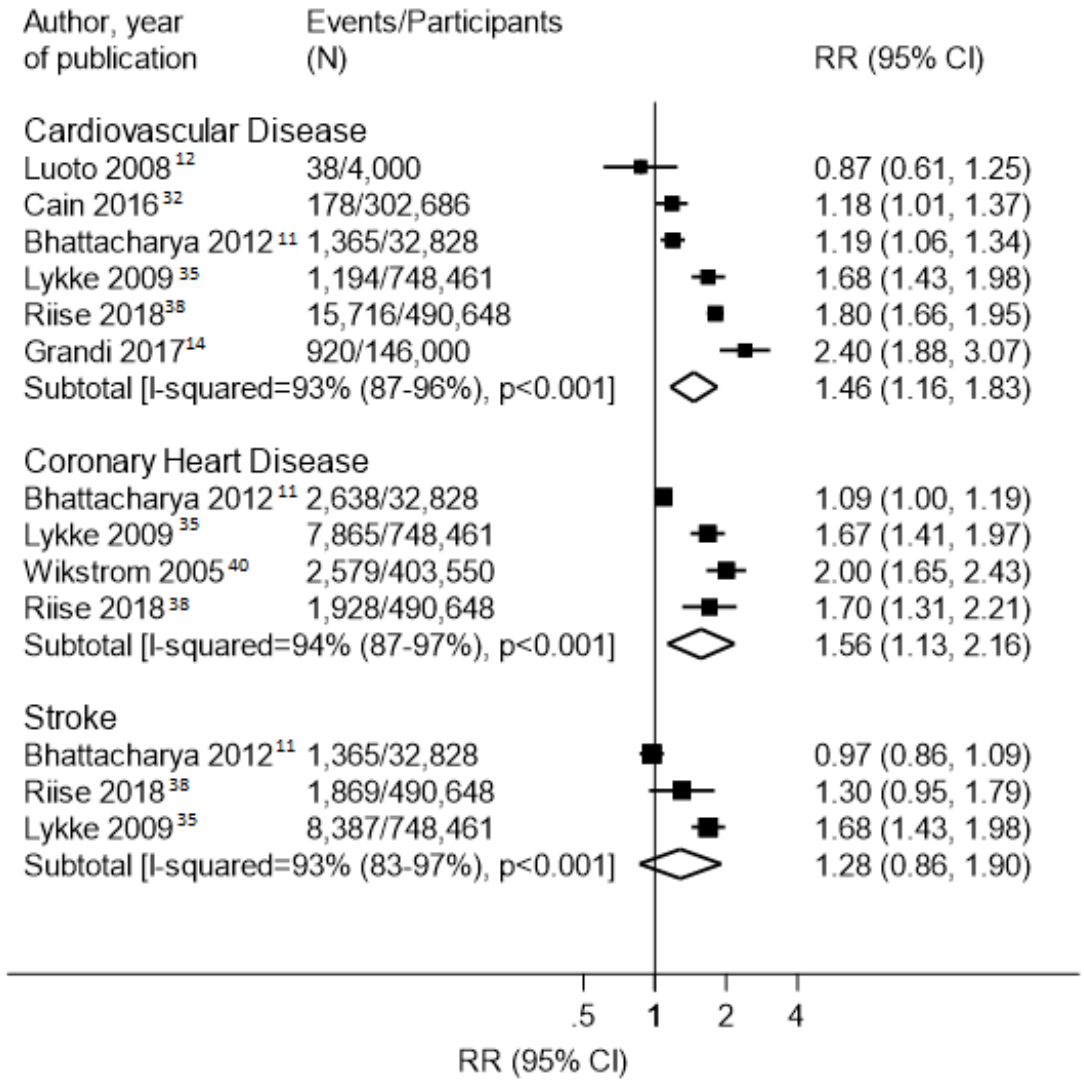
Table S10. Stratified Analyses of the Risk of Cardiovascular Disease Estimated from the Adjusted Meta-analyses.

Exposure	Strata		Studies (N)	RR (95% CI)	I^2 (95% CI)	P-value
GH in 1st pregnancy	Level of Adjustment	Adequately/Well	5	1.38 (1.26-1.52)	91% (83-96%)	0.796
		Poor	2	1.60 (1.50-1.72)	82% (53-93%)	
	Risk of Bias	Low Risk	5	1.51 (1.42-1.60)	93% (87-96%)	0.904*
		Not Low Risk	2	1.75 (1.43-2.14)	94% (82-98%)	
	Average follow-up	<20 years	4	1.63 (1.53-1.74)	93% (86-96%)	0.281
		>20 years	3	1.21 (1.08-1.36)	63% (0-92%)	
	Year of Publication	Up to 2010	3	1.50 (1.32-1.71)	80% (35-94%)	0.781
		2010 onwards	4	1.53 (1.44-1.62)	96% (92-98%)	
	Population	European	5	1.61 (1.51-1.71)	91% (81-95%)	0.694*
		Non-European	2	1.20 (1.06-1.36)	95% (83-98%)	
A history of GH	Level of Adjustment	Adequately/Well	3	1.34 (1.24-1.46)	87% (64-96%)	0.417
		Poor	4	1.41 (1.21-1.65)	82% (53-93%)	
	Risk of Bias	Low Risk	4	1.31 (1.21-1.43)	66% (1-88%)	0.656*
		Not Low Risk	4	1.50 (1.29-1.74)	91% (76-96%)	
	Average follow-up	<20 years	3	2.40 (1.77-3.27)	0% (0-90%)	0.475
		>20 years	5	1.31 (1.22-1.42)	83% (57-93%)	
	Year of Publication	Up to 2010	3	1.28 (1.08-1.52)	89% (56-97%)	0.863
		2010 onwards	5	1.37 (1.27-1.48)	83% (61-93%)	
	Population	European	3	1.27 (1.18-1.38)	70% (0-91%)	0.303*
		Non-European	5	1.90 (1.58-2.28)	72% (20-90%)	

CI – Confidence Intervals; GH – Gestational Hypertension; RR – Relative Risk; N - Number

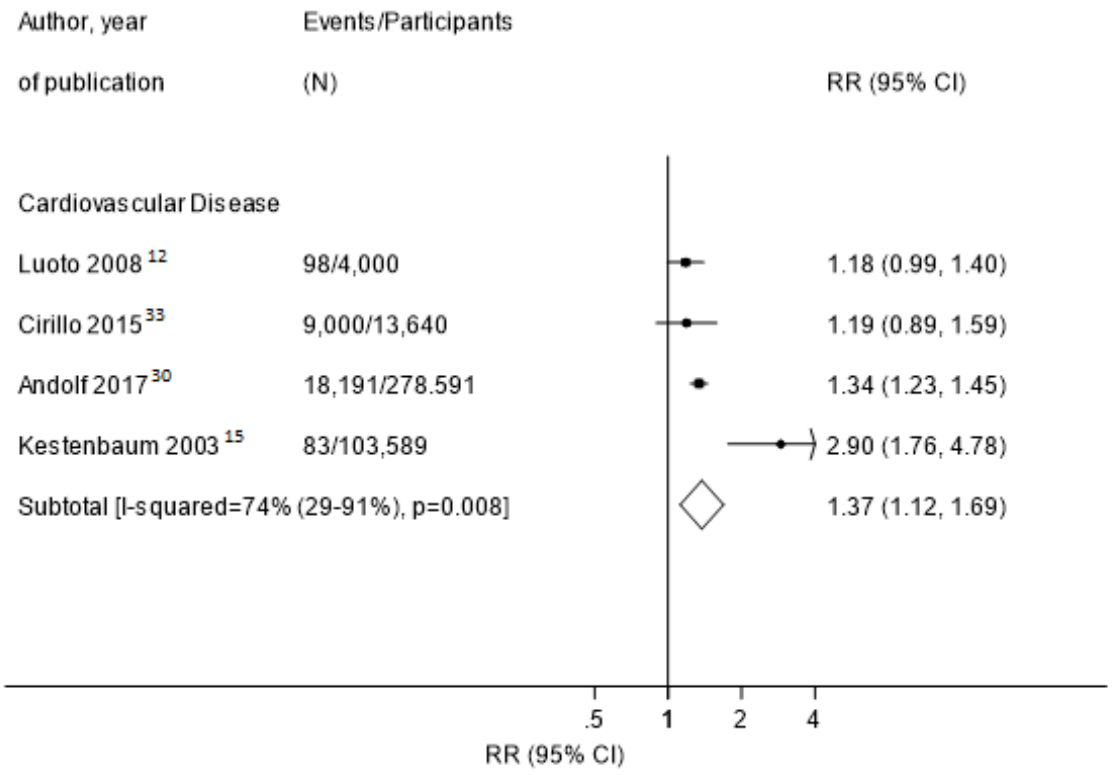
* Test for interaction, all other – values are test for trend from meta-regression

Figure S1. Association between gestational hypertension in a woman's first pregnancy and subsequent risk of cardiovascular events in unadjusted analyses.



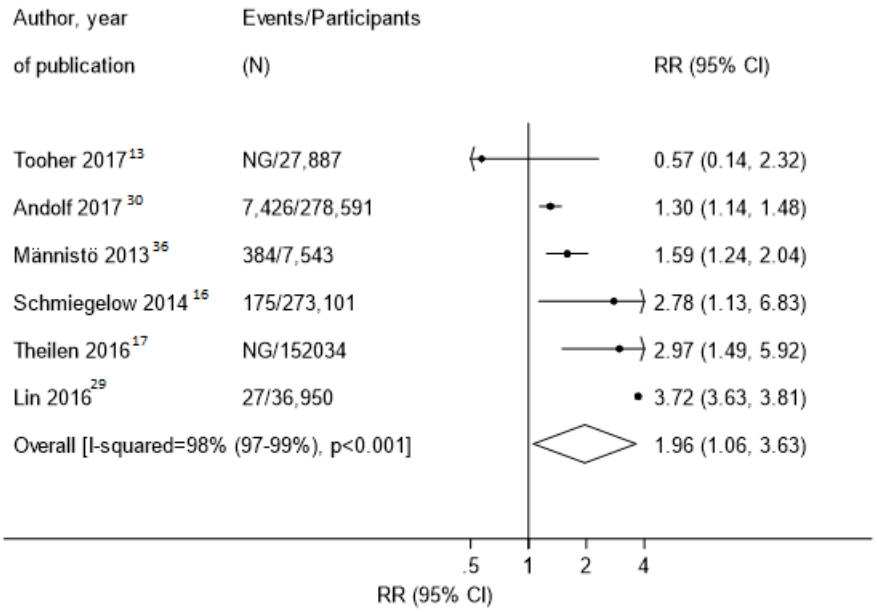
CI – Confidence intervals; RR – Relative Risk

Figure S2. Association between a history of one or more pregnancies affected by gestational hypertension and subsequent risk of cardiovascular events in unadjusted analyses.



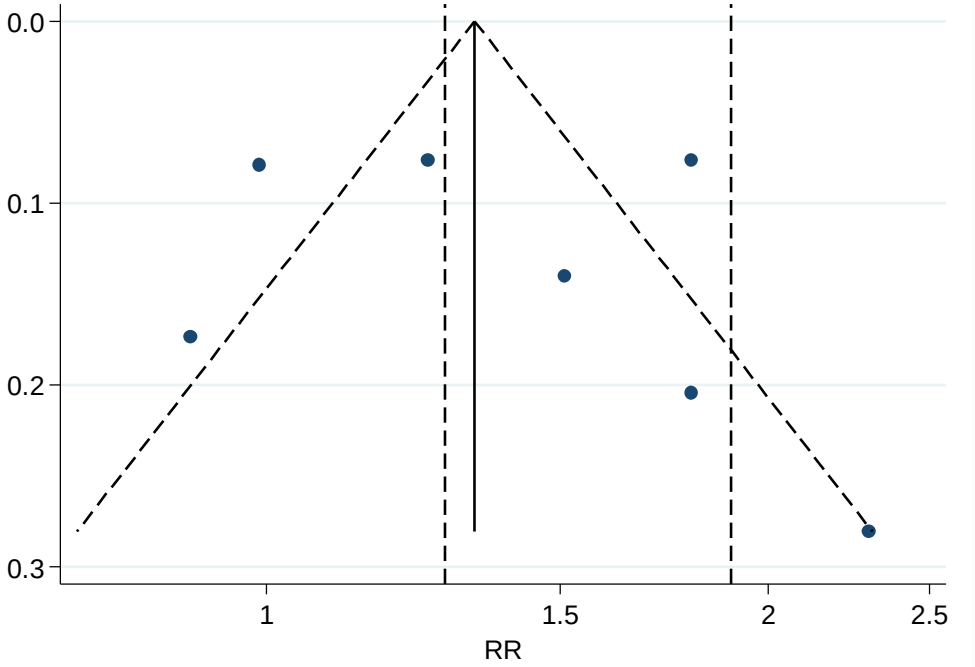
CI – Confidence intervals; RR – Relative Risk

Figure S3. Association between a history of one or more pregnancies affected by gestational hypertension and subsequent risk of any stroke event in adjusted analyses.



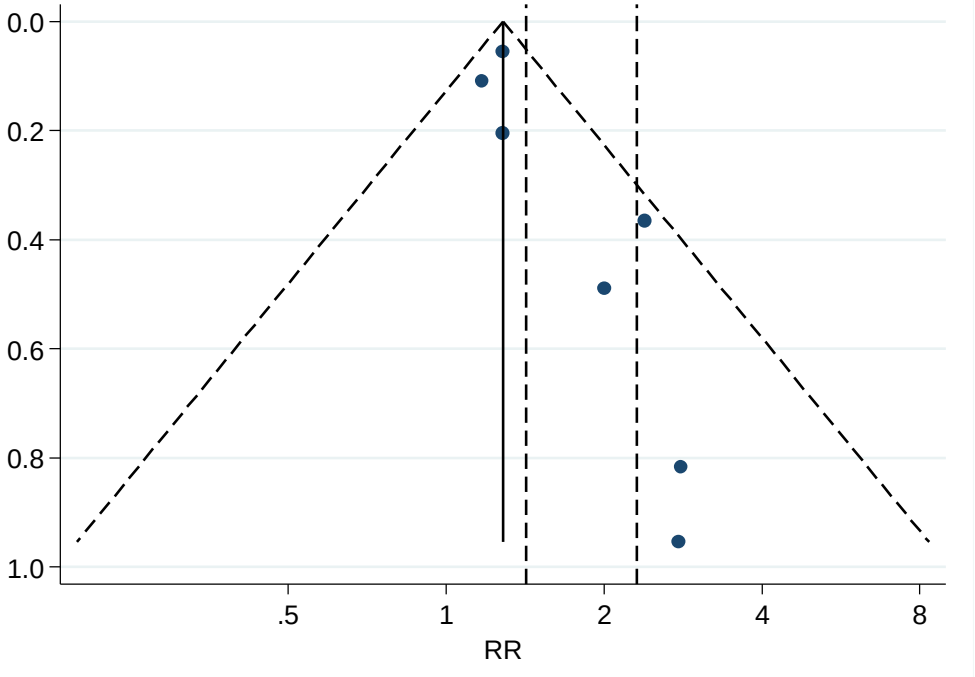
CI – Confidence intervals; NG – not given; RR – Relative Risk

Figure S4. Funnel plot of the studies contributing to the meta-analysis of the risk of cardiovascular disease after gestational hypertension in the first pregnancy.



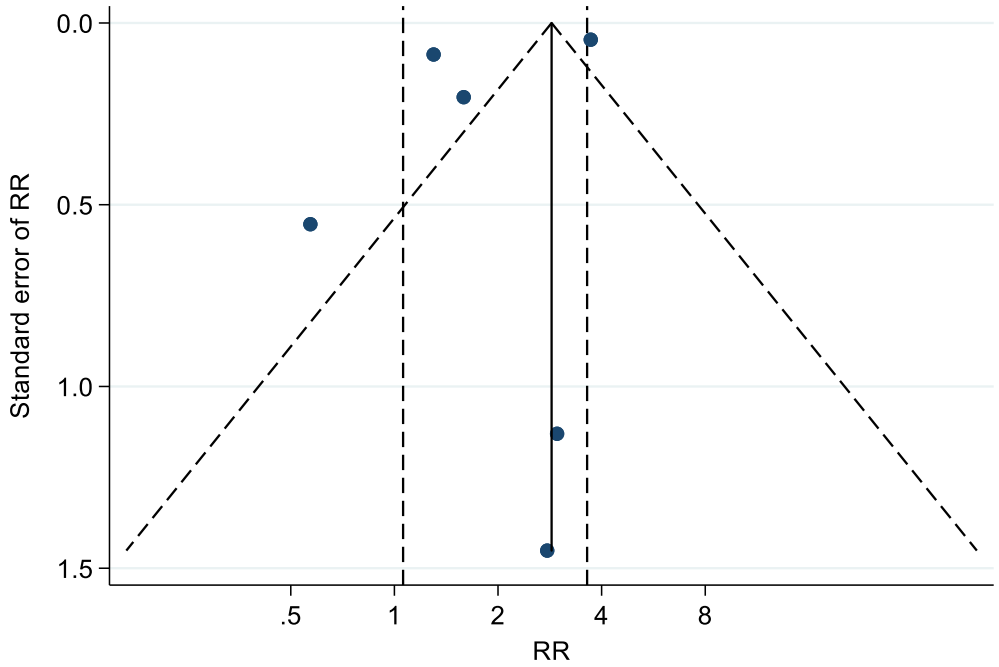
Egger's test p-value: 0.682. Vertical dashed lines indicate the confidence intervals from the pooled analysis. RR- Relative Risk

Figure S5. Funnel plot of the studies contributing to the meta-analysis of cardiovascular disease risk after a history of one or more pregnancies affected by gestational hypertension.



Egger's test p-value: 0.051. Trim-and-fill estimate: RR=1.26 (1.15-1.39). Vertical dashed lines indicate the confidence intervals from the pooled analysis. RR- Relative Risk

Figure S6. Funnel plot of the studies contributing to the meta-analysis the risk of any stroke event after a history of one or more pregnancies affected by gestational hypertension.



Egger's test p-value: 0.382. Vertical dashed lines indicate the confidence intervals from the pooled analysis. RR- Relative Risk